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SMS 201-995 IN THE MANAGEMENT OF PORTAL HYPERTENSION

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A Thesis submitted for the degree of

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to the

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Presentations and Publications

Parts of this work have been presented to learned societies. These presentations are listed below.

1) The Effect of SMS 201-995 on portal and systemic haemodynamics in cirrhosis.
Association of Surgeons of Great Britain and Ireland
April 1987.

2) SMS 201-995 in portal hypertension.
Glasgow Gastroenterology Club, June 1987.

3) SMS 201-995 in the management of variceal bleeding.
British Society of Gastroenterology, September 1987.

The following papers have been submitted for publication or accepted for publication.

1) The effect of SMS 201-995 on portal and systemic haemodynamics in cirrhosis. McKee RF, Pringle SD, McKee RF, Pringle SD, Garden OJ, Lorimar AR and Carter DC.
Accepted for publication by Alimentary Pharmacology and Therapeutics.

2) The use of oesophageal tamponade in the management of variceal bleeding.
Haddock G, McKee RF, Garden OJ, Anderson JR and Carter DC.
Submitted to Digestive Diseases and Science.

These studies were performed between August 1986 and July 1988 when I was a registrar in the University Department of Surgery, Royal Infirmary, Glasgow.

I declare that I am the sole author of this thesis. All the studies were planned and carried out by myself except as acknowledged above. Where assistance has been obtained from others, such help has been freely acknowledged.

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SUMMARY OF THESIS

Bleeding from oesophageal varices is one of the most serious emergencies seen in medical practice. Control of the bleeding is the first priority but neither of the two treatments commonly used today, oesophageal tamponade or intravenous vasopressin, is ideal. Oesophageal tamponade can give control of bleeding in more than 90% of cases (1) but may cause aspiration pneumonia or respiratory arrest and certainly causes considerable discomfort to the patient. Vasopressin is hardly less unpleasant and carries the risk of myocardial infarction and cardiac arrest (2,3). Therefore a new drug for the temporary control of bleeding from oesophageal varices would be useful. There is evidence that naturally occurring somatostatin is at least as effective as vasopressin in this regard and has no major side-effects (4,5) but its short half-life and instability in solution are disadvantageous. SMS 201-995 is a new long-acting analogue of somatostatin with a plasma half-life of 45 minutes and which is stable in solution (6). Little work has been done using this analogue and in particular it has not been assessed in a clinical trial of treatment of bleeding varices. This thesis sets out to examine the effects of SMS 201-995 in patients with portal hypertension and in two rat models of portal hypertension. The literature on portal hypertension is reviewed with particular reference to the

management of bleeding oesophageal varices.

Chapter 2 consists of a retrospective study of oesophageal tamponade in the management of variceal bleeding, assessing its efficacy in bleeding control as well as the complications encountered.

In Chapters 3 to 7, three studies using SMS 201-995 are reported. The acute effects of SMS 201-995 on portal and systemic haemodynamics were measured in stable cirrhotic patients and this is described in Chapter 3. Cardiac output and systemic vascular resistance were measured using the thermodilution method and portal pressure was assessed by measuring the wedged and free hepatic venous pressures. Thereafter work proceeded in two areas simultaneously. Chapters 4 to 6 describe studies of the effects of SMS 201-995 in normal rats and in two rat models of portal hypertension. A rat model of extra-hepatic portal hypertension, using partial portal vein ligation, and a rat model of cirrhosis, induced by carbon tetrachloride, had been established and characterised previously in the University Department of Surgery, Glasgow Royal Infirmary (7). These models were used to study the effects of SMS 201-995 on systemic haemodynamics, portal pressure and portasystemic shunting. A radioactive microsphere method was used to measure blood flow and portasystemic shunting.

Running concurrently with this animal study a controlled clinical trial was undertaken to compare the efficacy of SMS 201-995 with that of oesophageal tamponade in active

variceal bleeding. This trial is described in Chapter 7. The efficacy of both treatments with regard to control of bleeding was studied along with their complications and side-effects, in 40 episodes of variceal bleeding.

In Chapter 8 conclusions are drawn from the results of these studies and the work is placed in the context of other recent work in therapy for portal hypertension. A number of questions are raised by this work and several avenues for further investigation are suggested.

CHAPTER 1

HISTORICAL REVIEW

An understanding of the pathophysiology of a disease process is crucial to the development of treatment for that disease. Over the years there has been much discussion of the pathophysiology of portal hypertension and it is still incompletely understood.

In 1826 Laennec described the appearance of the liver in chronic liver disease and coined the term "cirrhosis" (8). He stated that "its development in the liver is one of the most common causes of ascites". The Russian surgeon Eck, who gave his name to the first experimental portacaval shunt operation, was also intrigued by the development of ascites in chronic liver disease and felt that this was due to an obstruction to flow within the liver (9). Interest in bleeding rather than ascites as a manifestation of portal hypertension developed over the ensuing years so that Prebble was able to review the world literature on bleeding varices in 1900 (10). By that time the presence and position of varices, their role as shunts and their propensity to bleed had been established.

Three central questions regarding the pathophysiology of portal hypertension have been posed over the years. Firstly, what is the cause of the chronic increase in portal pressure? Secondly, why do only some patients with portal hypertension develop oesophageal varices? Thirdly, why do oesophageal varices bleed?

The cause of the chronic increase in portal pressure.

In terms of fundamental understanding of the disease process, the first is the most important question. Two opposing theories have developed. The first, perhaps more obvious theory, is the "obstruction" or "backward flow" theory. Obstruction was suggested as the cause of ascites in patients with portal hypertension by the early workers. Drummond and Morrison published a post-mortem study of patients with cirrhosis in 1896 (11) and stated that the presence of shunts in cirrhosis correlated with the absence of ascites which developed secondary to obstruction. Vidal also proposed in 1903 (12) that "consequent to scarring, the calibre of the intrahepatic ramifications of the portal vein decreases, portal tension increases". The opposing theory, the "forward flow" theory, was suggested initially by Banti's comments on his patients with congestive splenomegaly in 1894 (13). Studies by Herrick, published in 1907 (14), supported the concept that an increased inflow into the portal system was the cause of portal hypertension. Herrick's experiments demonstrated that portal pressure rose with increasing arterial pressure and that this effect was more marked in the cirrhotic liver. During the first few decades of this century, therefore, the forward flow theory held sway but since then the backward flow theory has been more prominent. This swing was perhaps initiated by McIndoe of the Mayo Clinic who reported a histological study in 1928, describing hepatic cellular destruction, regenerating

nodules, sclerosis and the development of collateral venous channels (15). He thus emphasised the role of obstruction. Over the next 30 years the backward flow theory was supported by a number of workers who observed that the blood flow in the portal vein in portal hypertension was not increased. The first proponent of the portacaval shunt in humans, Whipple, supported this theory because of McIndoe's work on liver histology and work of his own showing histological evidence of back pressure in the spleen in portal hypertension (16). In 1952 Bradley reported a decrease in blood flow in the portal vein in portal hypertension (17) and this finding was confirmed in cirrhotic patients by Moreno and colleagues (18). They calculated that increased resistance to splanchic blood flow must therefore be present. However in the past 30 years the forward flow theory has re-emerged. In 1959 Tisdale and colleagues reported the occurrence of portal hypertension and bleeding oesophageal varices in the absence of obstruction (19) and around the same time Sherlock's group were emphasising the hyperdynamic circulation in patients with liver disease (20). Witte and colleagues' experiments in dogs (21) subsequently supported the theory of increased splanchnic blood flow in portal hypertension, and with the advent of thermodilution techniques for the measurement of cardiac output (22) further confirmation of the increased cardiac output and decreased systemic vascular resistance has been obtained (23). Two groups have contributed very

significantly in the last five years. Groszmann's group (24,25) have developed an experimental model of portal hypertension in the rat using partial portal vein ligation, and with the use of microsphere techniques have demonstrated the existence of a hyperdynamic circulation with an increase in the blood flow into the portal system, termed the portal venous inflow. Portal venous inflow is made up of the venous drainage of all splanchnic organs which is then distributed between the portasystemic shunts and the portal vein. The use of radioactive microsphere techniques has meant that shunt blood flow, portal vein flow, total hepatic flow and portal venous inflow can all be measured and this has given a more comprehensive picture of haemodynamics in the portal hypertensive rat. Benoit's group (26) have used a similar model and methods but have added a mathematical model to try to assess the relative contribution of the 'forward' and 'backward' flow components to the portal hypertension. Their prediction is that the forward and backward flow mechanisms account for 40% and 60% of the increase in portal pressure respectively.

In clinical terms the backward flow theory of portal hypertension has been correlated with the histology of liver disease in that the height of portal venous pressure does seem to correlate with the degree of nodule formation in the liver (27). There is a poor correlation with the apparent degree of cirrhosis and in particular of fibrosis (27). Theories about the cause of the increased portal venous

inflow proposed in the forward flow theory abound and at present the gastrointestinal hormone glucagon seems the most likely candidate as the mediator of this process (28,29,30).

The distribution of collateral flow.

The question of why only some patients with portal hypertension develop oesophageal varices has not been adequately answered. The existence of a collateral circulation in response to liver disease has been known since the last century (11) and variability in the development of collaterals in different areas of portasystemic anastomoses has also been known (31). Modern radiological techniques have shown that there is great variation in the degree of portasystemic shunting and in the distribution of the shunts. Groszmann and colleagues (32) used isotope studies and contrast radiology to demonstrate that 16% of biopsy proven cirrhotics had no discernable portasystemic shunting while 39% had complete shunting. Britton (33), in a study of 92 patients with portal hypertension, noted that two main patterns of distribution of collaterals existed. Patients with a predominant coronary- azygous vein collateral pattern had a high incidence of significant oesophageal varices associated with greater risk of bleeding and severity of bleeds. In the other patients the most common collaterals were in the regions of the inferior mesenteric vein, the splenic and renal veins and the umbilical veins. The cause of this variation is unknown.

The cause of variceal bleeding

Perhaps the most practical question with regard to the pathophysiology of portal hypertension is why do oesophageal varices bleed? Two theories predominate, the theory that varices are eroded from without due to acid from the stomach and the theory that varices disrupt due to internal factors.

In 1945 Baronofsky and Wangensteen (34) published an animal experimental study in which they showed that obstruction of the splenic vein increased susceptibility to peptic ulceration and erosions and they suggested that erosion by acid was a significant factor in the causation of variceal bleeding. Wangenknecht (35) studied 44 autopsy specimens some years after the patients' death from variceal bleeding and found evidence of oesophageal inflammation and ulceration in 19 cases. A similar study by Chiles et al (36) showed oesophageal ulceration in 45 of 80 cases. However in 1963 Orloff and Thomas (37) undertook a histological study of oesophageal biopies in patients who had had surgery for variceal bleeding within eight hours of admission to hospital. They found little evidence of oesophagitis and concluded that the erosion theory was unlikely to be true. They felt that the previous studies (35,36) had the disadvantage that they were performed on tissue removed from the body some time after the onset of bleeding and pointed out that varices do bleed in low acid states, since the majority of patients with cirrhosis have a very low gastric acid output (38). Since then a number of studies have been

published to support the view that erosion of varices by acid is not a major factor causing bleeding. There is no increase in the incidence or length of reflux episodes in patients who have bled from varices compared to normals and lower oesophageal sphincter pressure does not differ significantly from that in the normal patient (39,40). Several further histological studies have failed to show evidence of significant inflammation of the oesophagus in patients with bleeding from varices. (41,42). A controlled clinical trial has shown that the H_2 receptor antagonist cimetidine, which reduces gastric acid output, had no effect on the rate of recurrence of variceal bleeding (43) and this finding also helps to weaken the erosion theory. The theory that varices disrupt due to internal factors therefore seems more plausible.

It was noted some years ago that patients with large varices had a higher risk of bleeding than those with small varices (44). The law of Laplace states that the tension in the wall of a cylindrical vessel is proportional to the radius and thus varices of greater diameter might be more likely to bleed because of increased wall tension. The association of variceal size with bleeding has been confirmed in recent years (45) but studies of portal pressure in cirrhotic patients have generally failed to associate the level of portal pressure with risk of bleeding (45,46). It seems that an increased portal pressure is necessary before varices develop but that above this level

the height of pressure is not related to bleeding. In 1951 Butler reported studies of the anatomy of the veins of the oesophagus (47) and interest in this subject as part of the explanation why varices bleed has revived in recent years. Four layers of veins have been identified and all channels are found to be significantly dilated in patients with varices. It is felt that the deep intrinsic veins are those which form the varices seen at endoscopy (48) and the red wale markings and cherry-red spots reported as signifying high risk of bleeding by Japanese workers (49,50) may represent more superficial channels. As long ago as 1900, Prebble (10) noticed that varices tended to bleed at the area of the gastro-oesophageal junction and the few centimetres above this rather than higher in the oesophagus. The work of Spence and colleagues (51,52) showing that in this region a large number of venous channels lie very near the mucosal surface, may provide an explanation for this observation. The presence of perforating veins with incompetent valves at the lower end of the oesophagus has also been suggested by the use of endoscopic ultrasound (53). The turbulent flow in these areas may increase the risk of rupture of varices at the lower end of the oesophagus.

In more general terms, poor liver function increases the risk of bleeding from varices (54,55,56) and also increases the risk of gastrointestinal bleeding from other sources such as gastritis (57). Liver function has a strong

influence on the prognosis in variceal bleeding (58,59). In 1964 Child described a classification system for patients with cirrhosis which depended on the severity of jaundice, ascites and encephalopathy along with serum albumin and nutritional state. This gave a good guide to prognosis. The classification used in this thesis is a modification of Child's grading by Pugh and colleagues (58) which is based on the prothrombin time, serum albumin and bilirubin and the presence of ascites and encephalopathy. Patients with cirrhosis are placed in grades A, B or C, with progressive worsening of liver function. Modified Child's grade A patients have a significantly better prognosis than grade C patients after a variceal bleed. Garden and colleagues reported that in a study of 81 bleeds from oesophageal varices in 62 patients, three patients in modified Child's grade A on admission all survived, while 37% of 44 modified Child's C patients died during that admission (60). The underlying cause of the portal hypertension also influences the prognosis. Patients with varices due to portal vein thrombosis have a higher risk of bleeding but a better survival prospect (61). It is generally agreed that continued alcohol abuse carries a higher risk of rebleeding and mortality (62,63), though an accurate history of alcohol intake is difficult to obtain (64). The development of a hepatocellular carcinoma as a complication of cirrhosis carries a high risk of variceal bleeding (63).

THERAPY - THE ACUTE BLEED

Therapy for portal hypertension and oesophageal varices can be divided into the management of the acute bleed and the prevention of rebleeding. Over the years there has been some overlap between these two aspects because of the era of emergency shunt surgery and the opposing attitude that treatment for the acute bleed was sufficient intervention in these poor risk patients.

Diagnosis and general measures

The patient frequently presents with significant haematemesis or melaena from an unknown source. Clinical assessment and simple laboratory estimations may be a guide to the amount of blood loss. Mailer and colleagues (65) reported that a 1200ml blood loss causes a tachycardia of more than 100 beats/minute accompanied by pallor and postural hypotension, and that a serum urea of more than 8.5 mmol/l in the presence of a normal creatinine in upper gastrointestinal bleeding probably indicates that at least one litre of blood has been lost from the upper gastrointestinal tract (66).

With the advent of fibreoptic endoscopy initial resuscitation can be followed by early diagnosis of the source of bleeding. Several studies (67,68,69) have established that up to 40% of patients with varices bleed from other lesions in the gastrointestinal tract, and accurate diagnosis by means of endoscopy is therefore essential. Large varices with overlying inflammation and red spots or weals on the mucosa are more likely to be the cause of bleeding than small pale varices (50). The problem of bleeding from gastric varices is not considered in detail in this thesis since this is much less common. Bleeding from gastric varices is difficult to diagnose and most centres have managed such bleeding by means of undersewing of the varices at operation. A recent report describes the use of a combination of intravariceal and paravariceal sclerotherapy

for the control of such bleeding (70).

Once the diagnosis is established further resuscitation and measures to prevent complications are instituted. Since blood transfusion has been available this has been the sine qua non of the treatment of bleeding and large volumes of blood may be necessary (2). Bleeding from oesophageal varices is often associated with significant pre-existing coagulation defects due to chronic liver disease. These coagulation defects may be due to thrombocytopenia secondary to hypersplenism, depressed synthesis of the vitamin K dependent prothrombin complex factors or a chronic, low-grade disseminated intravascular coagulation (71). Pre-existing clotting disorders will be worsened by blood transfusion. Fresh frozen plasma is often given since any correction of the coagulation defect possible with vitamin K takes more than 24 hours. Platelet transfusions may be used if the platelet count is less than $80,000 \times 10$ /ml though the transfused platelets will be rapidly destroyed by the spleen. Antithrombin III and fibrinolytic inhibitors may reduce ongoing disseminated intravascular coagulation (71).

Hepatic encephalopathy is a serious complication of gastrointestinal bleeding in patients with liver disease and patients with this complication have a poor prognosis (72). Bowel washouts may be performed to reduce the protein load in the gut. Neomycin has been used in the treatment and prevention of hepatic encephalopathy for 30 years (73) since it reduces the load of ammonia producing bacteria in the

gut. Metronidazole seems to have similar efficacy (74). Lactulose is broken down in the caecum to lactic and acetic acid and the resulting drop in faecal pH suppresses the growth of ammonia forming bacteria. Lactulose and neomycin were shown to be of equal efficacy by Conn's group (75) and the use of lactulose and neomycin together has been shown to be of benefit in one study (76). There is a significant incidence of bleeding from gastric erosions and stress ulcers in these severely ill patients and MacDougall and colleagues have shown that an H_2 receptor blocker reduces this complication (77).

Control of bleeding

25-40% of variceal bleeds stop spontaneously (2,78), but when this does not occur measures to control the bleeding are needed.

i)Oesophageal Tamponade

The principles of balloon tamponade in the arrest of variceal haemorrhage were described as far back as 1900 (10). Sporadic reports of this method of treatment appeared thereafter but it became established with the development of the Sengstaken Blakemore tube in the 1950's (79). This tube had three lumens - two leading to balloons which were inflated in the stomach and oesophagus respectively and one lumen which was used to aspirate the stomach. Shortly after this Linton and Ellis (80) described a tube with a single large gastric balloon and it has been suggested that the efficacy of either tube depends on occlusion of the veins by pressure at the gastro-oesophageal junction. Despite the development of a four lumen tube to enable the aspiration of both upper oesophagus and stomach (81), the use of balloon tamponade has been criticised, particularly in the United States. In 1967 Conn and Simpson (82) reported that tamponade with a three lumen tube achieved control of bleeding in only 56% of 40 patients and had a 35% incidence of major complications. Others argue that these reports are due to the use of balloon tamponade with a three lumen tube in less than ideal situations, where it is undoubtedly dangerous (83,1). In 1971 Pitcher reported that bleeding was

controlled in 46 of 50 patients treated with oesophageal tamponade with only two major and seven minor complications (83).

Despite its efficacy in controlling bleeding balloon tamponade has obvious disadvantages: it is unpleasant for the patient and even in the best hands the risk of aspiration and chest complications cannot be completely eliminated. In Pitcher's group of 50 patients the one patient who died after oesophageal tamponade had evidence of aspiration of blood into the trachea (83). The control of bleeding by less invasive means is therefore an attractive prospect and various drugs have been used for this purpose.

ii) Drugs

a) Vasopressin

The first drug used for treatment of active variceal bleeding was vasopressin (84) and this has remained the drug in common use. Studies by Shaldon and colleagues (85) established that it causes a significant fall in portal pressure. Texter's studies in dogs showed that this effect is due to vasoconstriction which is most marked in the small vessels (86). However although its vasoconstrictor effect is most pronounced in the skin, gut and skeletal muscle (87), vasopressin is a generalised vasoconstrictor and it therefore causes a concomitant increase in systemic arterial pressure and decrease in cardiac output. Several placebo controlled trials of its efficacy in active variceal bleeding have been performed. In 1962 Merigan and colleagues (88) achieved bleeding control on 16 of 29 occasions when patients with clinically bleeding varices were treated with 20 units of vasopressin over 20 minutes in comparison to 24 occasions when patients were treated with placebo and all continued to bleed. Unfortunately during this study endoscopy was not available to confirm the diagnosis and assessment of continued bleeding was inadequate in some cases. Conn and colleagues(2) used intra-arterial vasopressin infused into the superior mesenteric artery and gained control of bleeding in 12 of 17 patients treated with vasopressin and conservative treatment in comparison to 4 of 16 patients treated with conservative treatment only. This

study is difficult to assess because conservative treatment included oesophageal tamponade in an undefined number of patients. The most recent placebo controlled trial (89) failed to show a difference in bleeding control rate between the vasopressin and placebo treated groups. None of these trials showed an improvement in survival in patients treated with vasopressin.

Because of its mode of action, vasopressin has significant side-effects. It has been shown in both animals (90) and man (91) that vasopressin reduces cardiac output and myocardial infarction as a complication of vasopressin therapy was first reported in 1951 (3). Vasopressin also contracts the smooth muscle of the gut wall, causing abdominal colic, and ischaemic problems in the skin have been reported (92).

To try to reduce these problems and increase its effectiveness various means of administering vasopressin have been tried. In a study in 25 patients with bleeding varices by Johnson and colleagues (93), infusion directly into the superior mesenteric artery did not improve efficacy or reduce generalised side-effects but increased local problems because of the more complex catheter insertion. On the other hand a study of 31 episodes of variceal bleeding by Sagar and colleagues (94) where 16 patients received 20 unit intravenous boluses of vasopressin every 2-4 hours and 15 patients received peripheral intravenous infusion at 0.4 units/minute showed a significant advantage for continuous infusion since 13 patients in this group stopped bleeding in

comparison with two in the group given boluses. Continuous peripheral intravenous infusion is now the most common means of administration of vasopressin.

Combination of vasopressin with other agents may reduce possible side-effects. Isoproterenol, a cardiac inotrope and peripheral vasodilator, seems to be effective in reducing cardiac side-effects (95) but increases in portal pressure have been reported (95). The peripheral vasodilators nitroprusside (96), nitroglycerin (97) and isosorbide dinitrate (98) probably further reduce portal pressure. However although studies (96,97) have shown that nitroprusside and nitroglycerin reduce the systemic effects of vasopressin Hallemans and colleagues have failed to show any reduction in cardiac side-effects in stable cirrhotics by combining isosorbide dinitrate and vasopressin (99). The results of two controlled trials comparing vasopressin plus nitroglycerin with vasopressin alone have been published (100,101). Although there were differences in the dose of vasopressin, in the patient populations and in the route of administration of nitroglycerin (Gimson's group (100) gave intravenous nitroglycerin, Tsai's group (101) gave sub-lingual nitroglycerin), both studies showed improvement in bleeding control and reduction in side-effects in the vasopressin and nitroglycerin group. Despite this, no improvement in survival was seen.

Triglycyl vasopressin is a slow release formulation of vasopressin which can be given by intermittent intravenous

bolus rather than infusion. It was initially reported to have a selective action on the mesenteric circulation (102) but it has since been established that changes in cardiac function and systemic blood pressure are similar to these with vasopressin itself (103). The majority of reports (78,104) have been of a bleeding control rate similar to vasopressin, but one report demonstrated improved efficacy compared to vasopressin, giving rise to some doubt regarding the activity of the vasopressin used (105). Similar cardiac side-effects have been reported (104).

b) Propranolol

Propranolol has recently been advocated for use in portal hypertension because of the work of Lebrec and colleagues, who reported in 1980 (106) that it caused a significant drop in wedged hepatic vein pressure in cirrhotic patients. In 1967, Price and colleagues (107) had demonstrated that this effect was achieved by a reduction in splanchnic blood flow in normal subjects. Further studies showed that the effect was lessened but not eliminated when a cardioselective beta-blocker was given (108) and it can be concluded that the effect of propranolol is achieved via both a reduction in cardiac output and splanchnic vasoconstriction due to blockade of vaso-dilatory splanchnic beta-adrenergic receptors. However, propranolol has been used principally for prevention of rebleeding because of its cardiac and vascular side-effects which could cause difficulties in resuscitation of the actively bleeding patient. Its use in the prevention of rebleeding will be considered later.

c) Other vasoactive agents

Other adrenoreceptor blocking agents have been studied in stable cirrhotic patients but these have a lesser effect on portal pressure (109) and have not been used for actively bleeding patients. Nitrates as single agents have been studied for their effects on portal pressure but have not been used to control variceal bleeding. Cimetidine is commonly given to patients with active variceal bleeding. It has no effect on portal pressure (110) but has been shown to reduce the incidence of bleeding due to acute gastric erosions which are liable to develop in acutely ill patients (77).

d) Somatostatin

Somatostatin was first isolated and described by Brazeau and colleagues in 1973 (111) when it was identified as a tetradecapeptide with growth hormone release inhibiting effects. It soon became apparent that somatostatin was widespread in the body with particularly significant action in the gut. Bloom and colleagues described the reduction of food-induced plasma gastrin rise by somatostatin in 1974 (112) and further investigation revealed its effect in reducing splanchnic blood flow in normal man in 1976 (113). Somatostatin blocks insulin and glucagon release, blocks the effects of cholecystokinin and secretin, delays gastric emptying and has a potent effect on gastric acid secretion. The output of all other known circulating gastrointestinal hormones is blocked by somatostatin (114).

Initial animal work in dogs, using electromagnetic flow probes attempted to elucidate its mode of action in reducing splanchnic flow (115,116). It appeared to reduce portal vein flow by means of pre-splanchnic vasoconstriction and this effect appeared to be selective. Reports that somatostatin infusion was effective in controlling bleeding in peptic ulcer haemorrhage (117) and in actively bleeding oesophageal varices (118) began to appear. Further investigation has confused the picture considerably. In normal man it has been demonstrated that somatostatin causes a fall in portal vein flow (119) without systemic haemodynamic effects (119,120) although this lack of systemic haemodynamic effect is

contradicted in one report in anaesthetised man (121). In cirrhotic patients the picture is less clear. In 1981 Bosch and colleagues (91) reported that somatostatin caused a significant drop in wedged hepatic vein pressure in cirrhotics while other workers (120,122) have reported no effect. These workers could demonstrate no effect on systemic haemodynamics during somatostatin infusion although Naeije and associates reported on two occasions (123,124) that intravenous infusion of somatostatin reduced the cardiac index as well as causing a short lived reduction in wedged hepatic venous pressure in patients with portal hypertension.

Attempts at elucidating these effects by means of animal experiments have also been contradictory. No change in cardiac index has been demonstrated in animals but contradictory effects on regional blood flow have been reported. Becker and colleagues (125) could show only a reduction in gastric and pancreatic blood flow with somatostatin whereas renal blood flow was increased, while Price and colleagues (126,127) showed a reduction in blood flow in all areas of the splanchnic circulation as well as in renal blood flow. Splanchnic effects seem to be mediated via the pre-splanchnic arterioles rather than the portal vein since injection of somatostatin into the portal vein produced no haemodynamic effect in rats (128).

Despite these contradictions, reports of the efficacy of somatostatin in upper gastrointestinal bleeding continue

(129) and in two controlled clinical trials it appears to be at least as effective as vasopressin in the control of active variceal bleeding (4,5). Clinical enthusiasm for its use seems to have been little affected by a recent report that the drug causes a significant reduction in renal plasma flow in man (130).

One of the major disadvantages of somatostatin is its extremely short plasma half-life of two to three minutes and this has stimulated the search for a long-acting analogue which is also more stable in solution. SMS 201-995 is a synthetic octapeptide analogue of somatostatin with a plasma half-life of 45 minutes following the termination of intravenous infusion (6). It is significantly more potent than somatostatin itself and has a greater relative effect on growth hormone release than on glucose and insulin metabolism and gastric secretion. One report has shown a reduction in portal vein flow, measured by electromagnetic flow meter, and portal pressure in rats (131) with no effect on systemic haemodynamics. It has also been reported, by the same group, to reduce portal vein flow and pressure in pigs (132) but systemic haemodynamic effects were recorded in these animals. In rats, SMS 201-995 stimulates the reticuloendothelial system (133), reduces the effects of endotoxaemia (134) and prevents the development of acute pancreatitis (135). Unlike somatostatin, it has been reported to increase urine flow in the dog (136). Burroughs and colleagues (137) could demonstrate no change in wedged

hepatic vein pressure in stable cirrhotics given various doses of SMS 201-995, but Wahren and Eriksson were able to show a reduction in liver blood flow and wedged hepatic venous pressure after SMS 201-995 (138).

There is therefore much that is unknown about somatostatin and, in particular, about its new long-acting analogue. The effect of SMS 201-995 on systemic and portal haemodynamics in human cirrhotics has not been confirmed. Its efficacy in the treatment of active variceal bleeding has not been investigated, and in particular comparison of the effects of a somatostatin infusion with those of more invasive treatments such as balloon tamponade has not been undertaken. Further investigation of the action of SMS 201-995 on regional and systemic haemodynamics may elucidate its potential benefits or side-effects in the cirrhotic patient.

iii) Injection sclerotherapy

The methods for control of active variceal bleeding which have been discussed so far exert only a temporary effect. Partly from a desire to integrate immediate control and definitive treatment and partly because in some patients bleeding is not controlled by the above methods, other more definitive methods have been used over the years. These will be discussed in more detail later.

The least aggressive of these methods is acute injection sclerotherapy. Injection sclerotherapy is obviously much more difficult technically in the presence of active bleeding but as expertise has developed it has been realised that this might be a very efficient method of stopping variceal bleeding (55). Terblanche in 1984 (139) reported the preliminary results of a trial assessing this method. 82% of bleeds were controlled by injection sclerotherapy. In his hands, the use of the rigid endoscope under general anaesthetic was associated with a lower incidence of technical problems, bleeding and aspiration than the use of the flexible endoscope. A recent retrospective review of injection sclerotherapy in the University Department of Surgery, Glasgow Royal Infirmary, has found that the rigid oesophagoscope is associated with a greater complication rate but confers no benefit in terms of reducing post-injection bleeding (140). Westaby and colleagues (141) have compared emergency sclerotherapy with the use of

vasopressin and nitroglycerin for control of active variceal bleeding. Although control of bleeding at twelve hours was significantly better in the sclerotherapy group no difference in the admission mortality or definitive control rate could be demonstrated. There is considerable interest in this method of treatment at present and the results of further clinical trials are awaited.

Transhepatic sclerotherapy was described by Lunderquist and Vang in 1974 (142) but although this method has been used in the treatment of actively bleeding varices (143), the radiological expertise required means that this is not a practical proposition in the majority of hospitals. Transhepatic sclerotherapy may be contra-indicated in many portal hypertensive patients with significant coagulopathy, often worsened by blood transfusion after a variceal bleed.

iv) Oesophageal transection

Before the development of the circular stapling gun, oesophageal transection for bleeding varices carried a very high mortality because of the need for thoracotomy. Pugh's report (58) of a 55% mortality even in 38 patients whose bleeding was controlled by other means for 24-36 hours so that they could be prepared for operation, is fairly typical. However, the advent of the automatic stapling gun caused a resurgence in enthusiasm for oesophageal transection as an emergency treatment for bleeding varices. One of the chief advocates of oesophageal transection is Johnston of Belfast and in 1982 he reported his results in 80 patients, 41% of whom were alcoholics (144). The overall mortality in this series was 14% but in the 19 emergency cases mortality was much higher at 32% and Johnston would now try to avoid oesophageal transection as an emergency procedure, preferring sclerotherapy. A report from the United States gives an even higher mortality of 89% in emergency operations (145) for uncontrolled bleeding.

v) Portasystemic shunts

The use of the portacaval shunt as an emergency treatment for active variceal bleeding was popular in the 1960's and 70's, particularly in the USA. Even in the hands of the most expert enthusiast the operative survival was only 58% in a series of all patients with variceal bleeding who had portacaval shunts performed within 7-8 hours of admission to hospital (146). The five year survival rate was 38% and encephalopathy occurred in nearly one third of the survivors. It is generally agreed that the risks of emergency portacaval shunt procedures outweigh the benefits of their efficient control of haemorrhage.

Therefore the control of acute variceal bleeding is still a problem. It seems likely that the treatment of choice over the next few years will be temporary control with one of the more selective drugs while injection sclerotherapy is being arranged as an emergency procedure.

The second aspect of the treatment of bleeding oesophageal varices is the prevention of rebleeding. It has been stated that 26% of patients who survive for two days after a variceal bleed will rebleed, if untreated, within six weeks (147). Each episode of variceal bleeding carries a mortality risk of between 25 and 50%. A study of the outcome in patients who had bled from oesophageal varices and who had no further treatment to prevent rebleeding has shown that at 12 months only 33% of patients survived (148). The prevention of rebleeding is obviously an important part of the treatment of these patients.

History

One of the first operations used in portal hypertension was omentopexy. Reported in 1898 by Talma and also described by Drummond and Morison (11) this became known as the Talma-Morison procedure. The parietal peritoneum was scarified and the omentum sutured to the raw surface in an attempt to stimulate the development of collateral flow. It seems that around 50% of patients had further gastrointestinal bleeding despite this procedure. An early alternative to omentopexy was splenectomy, originally advocated by Banti (13). These early operations formed the background to later development.

Two approaches to the prevention of rebleeding can be identified, the lowering of portal pressure and direct attack on the varices themselves. Over the years these approaches have been used in a variety of ways.

Portasystemic shunts

By redirecting the flow of blood from the high pressure portal system to the low pressure systemic venous system, portacaval shunting will lower portal pressure effectively. In the early part of this century Vidal performed the first portocaval shunt in a human (12) and this technique was used sporadically over the next few decades. Vidal had a good understanding of the pathophysiology of portal hypertension and described clearly the major problem of shunt surgery, encephalopathy. The first major report of the use of the portacaval shunt in a series of patients was by Whipple in 1945 (16), who described an end-to-side portacaval shunt using Blakemore's vitallium tube for the anastomosis. In subsequent decades, shunt surgery became established as a means of preventing rebleeding from varices. Over the years it has become clear that it is an effective means of preventing variceal bleeding but that it carries a high penalty. Operative mortality is significant, and is reported as between 7% (149) and 20% (150) for elective end-to-side portacaval anastomosis. The survivors have a 15-30% chance of developing hepatic encephalopathy (151), the major long-term complication of shunt surgery. A variety of operative techniques for portacaval shunting have been developed to try to improve the results.

The reports of the results of shunt surgery are often difficult to interpret. Many studies are retrospective and even those which are prospective controlled studies are open

to criticism. The source of gastrointestinal bleeding has not always been established, the cause of the cirrhosis has not been well documented, surgery has been performed at different times following an acute bleed and the results have been analysed in many ways. In one of the clearest reports Resnick and colleagues (152) looked prospectively at results of end-to-side portacaval shunt in alcoholic cirrhotics with upper gastrointestinal bleeding in comparison with medical treatment of bleeds alone. There was no statistically significant difference in survival, the medically treated patients dying of bleeding while the surgically treated patients died of hepatic failure. The five year survival rate was approximately 50% in a group of 79 patients where 42% were allocated to Child's grade A.

A mesocaval shunt was proposed in 1948 by Linton (153) to overcome the difficulties of portacaval shunting in children with portal vein thrombosis and in those adults who had had previous shunting. This was thought initially to function as a side-to-side shunt and was also recommended by Clatworthy and colleagues (154), particularly in children. The benefit of a side-to-side shunt was said to be continued perfusion of the liver but the fact that the anastomosis is between the high pressure portal venous system and the low pressure caval system means that blood flow is still hepatofugal. Further, arteriovenous fistulas in the liver may shunt blood from the hepatic arterial system to the portal venous system and this will also flow away from the liver. These concepts

were supported by a trial of end-to-side versus side-to-side portacaval shunts which demonstrated a higher incidence of post-shunt encephalopathy after side-to-side shunts (155).

A further attempt to design a shunt which maintains hepatic perfusion was the distal splenorenal shunt, described in 1967 by Warren (156). This shunt aims to selectively drain blood from oesophago-gastric varices by anastomosing the distal splenic vein to the left renal vein, leaving the spleen in situ. This is technically more difficult than an end-to-side shunt but the promise of a lower incidence of encephalopathy has attracted many surgeons in recent years. A recent survey of the prospective randomised trials of distal splenorenal shunt and portacaval shunt has shown no difference in long-term survival in alcohol cirrhosis (151). However it is felt that patients with non-alcoholic cirrhosis who have stable liver disease might well benefit from distal splenorenal shunt in terms of increased survival (157), although this has not been demonstrated in a randomised trial. The effect of distal splenorenal shunt on the incidence of encephalopathy is disputed, some studies showing a lower incidence of encephalopathy while others have failed to show a difference from portacaval shunt (151). In patients with portal vein thrombosis a distal splenorenal shunt may be possible where a portacaval shunt is precluded. One of the most recent types of shunt is an alternative selective shunt, anastomosing the left gastric vein to the vena cava (158). This has not been assessed in

Western patients with their high incidence of alcoholic cirrhosis.

Attempts to reduce the technical difficulty of shunt operations led to the use of a Dacron prosthesis (159). This resulted in the mesocaval interposition H graft which is technically easy but has a propensity for thrombosis (160). There has been a recent resurgence in interest in this technique (161), building on the idea that the fraction of the portal flow shunted will depend on the diameter of a synthetic graft used as the conduit for a portacaval shunt. It therefore should be possible to divert sufficient blood from the portal vein to reduce portal pressure without completely depriving the liver of its portal flow.

After a period of disillusionment with shunt surgery because of the appearance of encephalopathy in so many patients there has been some increase in interest in the British literature (162). However the majority of doctors continue to reserve shunt surgery for the elective prevention of rebleeding in a very limited number of patients, in general, young patients with non-alcoholic liver disease and good preservation of liver function. A recent report from India demonstrates that in extra-hepatic portal hypertension, if a distal splenorenal shunt is possible and remains patent, a good outcome can be expected (61).

Oesophageal transection

The alternative approach to prevention of rebleeding from varices is direct attack on the varices themselves.

Surgical ligation of the bleeding varices was an obvious solution which was suggested by Crile in 1950 (163). This was not effective in the prevention of rebleeding as all of his cases rebled within two years. Linton (80) also recommended transoesophageal ligation of varices but saw this as an emergency procedure to gain control of bleeding and thereafter prepared the patient for an elective portacaval shunt.

The direct approach developed in two directions with some surgeons combining the two techniques. Tanner performed a sub-cardiac gastric transection on a series of patients who had bled from varices and reported that eight of his 32 patients had major rebleeding following this procedure (164). Transection of the oesophageal mucosa alone was attempted (165) and some surgeons were even more aggressive and recommended total gastrectomy or oesophagogastrectomy (166). These major operations naturally had a high mortality rate. The most significant development in the field of transection/resection for treatment of oesophageal varices was the development of the circular stapling gun and Vankemmel of France was the first person to report its use for oesophageal transection in portal hypertension (167). In the United Kingdom Johnston from Belfast has been the main advocate of this method of treatment. He described his

indications for operation and technique in 1978 (168) and first reported a major series of 80 patients in 1982. The operative mortality rate was 14% and only one death from variceal bleeding occurred in the follow-up period of three years (144). A more recent report (169) includes 100 patients with a mortality rate of 15%. Child's C patients had a high mortality rate of 27%. In a follow-up period of up to seven years, 26 patients had recurrent gastrointestinal bleeding but only 11 were bleeding from varices and most bleeds were minor. Johnston carries out transection at the gastrooesophageal junction with meticulous devascularisation of the lowest 5 cm of the oesophagus. The left gastric vein is ligated at the upper border of the pancreas and the perioesophageal collaterals lying with the vagus nerves are also divided with any branches. He only performs splenectomy if the platelet count is below $50,000 \times 10$ /l.

The devascularisation of the oesophagogastric junction is much emphasised by Johnston and this is the second direction of development of the direct approach to oesophageal varices. It was advised at least as long ago as 1929 when workers from the Mayo Clinic described a case of coronary vein ligation (170). Tanner's sub-cardiac transection was accompanied by devascularisation of the upper half of the stomach (164). In the Far East there is significant interest in the Suguira procedure, in which extensive devascularisation is performed through a thoraco-abdominal

incision (171). Via the thoracotomy, transection of the thoracic oesophagus is performed and all dilated collateral venous vessels are divided. Further devascularisation of the oesophagus, cardia and lesser curve is performed in the abdomen, including ligation of the left gastric vessels along with selective vagotomy and pyloroplasty. Splenectomy is routinely performed. Suguira and his colleagues (172) have reported the results of this procedure in 671 patients. The overall operative mortality was 4.9% and the incidence of recurrent variceal haemorrhage was 1.5% over a follow-up period of up to ten years. Only 52 of the 671 patients in this group had alcoholic cirrhosis and there is some doubt about the ability of the Western alcoholic patient to withstand such a major procedure.

Injection sclerotherapy

The methods of prevention of variceal rebleeding discussed so far have all necessitated major surgery. This is obviously hazardous in many patients with portal hypertension and less invasive methods of control are therefore attractive. In 1939 Crafoord and Frenckner (173) described the injection of oesophageal varices with sclerosant solution during oesophagoscopy. Little interest was shown in this method for some years other than MacBeth's report of 30 cases in 1955 (174). However, interest increased rapidly following the report of Johnston and Rodgers in 1973 (175) of good control with few side-effects. Several prospective trials have confirmed that chronic injection sclerotherapy reduced the incidence of rebleeding from varices when compared with conservative medical management (176,177). Long-term survival rates are probably improved when patients treated with regular injection sclerotherapy are compared with the group treated with drugs and blood transfusion alone(176,178). Although Terblanche and colleagues (179) have reported that repeated injection sclerotherapy fails to improve survival, their study compared patients treated with repeated elective sclerotherapy to patients treated with sclerotherapy for variceal bleeds rather than only conservatively. Since there have been no other reports comparing these two treatments it is not clear whether regular sclerotherapy for obliteration

of varices confers a survival advantage over sclerotherapy only after variceal bleeds. Many other aspects of injection sclerotherapy, such as the optimal method, sclerosant and frequency of injection, are not well established.

When first described, sclerotherapy was performed using a rigid endoscope and this necessitated general anaesthesia. With the introduction of the fibreoptic endoscope it became possible to perform sclerotherapy under sedation. The use of the Williams sheath (180) around the flexible endoscope is a compromise between rigid and flexible endoscopy and a general anaesthetic may not always be necessary while using this method. For the injection of actively bleeding varices Terblanche has reported that the rigid endoscope and a general anaesthetic is preferable, causing fewer problems with bleeding and aspiration (139). Westaby and colleagues have compared the use of the sheath and the free-hand technique in varices injected soon after a bleed (181), and found that there was an increased incidence of bleeding problems with the free-hand technique, but most patients find the use of the sheath intolerable without a general anaesthetic. The majority of elective injection sclerotherapy is now performed under sedation with the flexible endoscope.

The type of injection has also been debated at length. Varices may be injected intravariceally or in the paravariceal region. Intravariceal injection causes obliteration of the lumen of the varix by sclerosant while

paravariceal injection causes thickening of the tissue overlying the varix. Bleeding from the varix is thus prevented for different reasons. Sclerotherapy was first described using the intravariceal technique but Paquet has been a strong exponent of the paravariceal technique in the last few years (182). It must be kept in mind that the division between the two techniques is at least partly artificial since Barsoum and colleagues (183) have shown that only 20% of intended intravariceal injections are totally intravariceal.

Little has been written about the large number of sclerosants used for injection of varices. Different sclerosing agents tend to be used by those who favour paravariceal injection (usually polidocanol) and those who use intravariceal injection (1.5% sodium tetradecyl sulphate(STD), 5% sodium morrhuate and 5% ethanolamine). Sodium morrhuate is difficult to obtain in the UK while ethanoleamine cannot be used in the USA. In animal studies Reiner showed (184) that STD was more thrombogenic than morrhuate and Blenkinsopp (185) showed that STD was more thrombogenic than ethanolamine. However Jensen (186) has reported a study in dogs in which although STD was one of the most effective sclerosants, the performance of ethanolamine and morrhuate varied with the site of the veins injected. In man, Gibbert (187) found a higher incidence of oesophageal ulceration and increased mortality in a group of patients treated with morrhuate compared to a group treated

with STD. Morrhuate has been associated with the development of adult respiratory distress syndrome in one report (188). 5% ethanolamine oleate is probably the most common sclerosant in the United Kingdom and a recent controlled trial found that injection with ethanolamine led to a lower rate of post injection bleeding and fewer oesophageal ulcers than injection with 2% STD (189).

The frequency of injection is another point of controversy. As discussed above, chronic injection sclerotherapy rather than sclerotherapy for acute bleeds only has been shown to reduce the number of rebleeds but improvement in survival has not been proven (179). During chronic injection sclerotherapy a trial from King's College Hospital has suggested that an increase in frequency of elective injection from the more common three weekly schedule to weekly has no effect on complication rate but reduces the bleeding rate (190).

The use of injection sclerotherapy is now well established. One report shows that of patients who survived an acute variceal bleed and were managed by chronic injection sclerotherapy, 67% survived for two years after their initial bleed (191). Bleeding was rare following variceal obliteration and a mean of 3.3 injections was needed to achieve obliteration.

Although the complications of sclerotherapy are usually minor in comparison with those of major surgery there are complications. Immediate problems with bleeding have been

reported with a frequency of 4-14% depending on how recently the varices have bled (181). Chest infection is probably the commonest complication (192) and is particularly associated with injection soon after a variceal bleed (140). During injection using the rigid oesophagoscope perforation is the most serious complication and formed the major complication in the series of 264 patients treated over twenty five years by Spence and colleagues (193), the incidence of perforation being 2.2%. Perforations are extremely rare when the flexible endoscope is used for injection (176). Ulceration of the oesophagus is reported to a varying degree depending on the frequency of endoscopy. Soderlund and Ihre (194) found ulceration in 8 of 57 patients who had sclerotherapy at 24 hours, one week, 3 weeks, 6 weeks and three months after a variceal bleed. McDougall and colleagues (176) found ulcers in 15 of 51 patients who had sclerotherapy at three weekly intervals till obliteration of varices was achieved. They found the more advanced complication of oesophageal stricture in 9 patients. In a study of 55 patients, Westaby and colleagues (190) noted an 80% incidence of ulceration when sclerotherapy was performed at one weekly intervals but only a 30% incidence when the interval between sclerotherapy sessions was three weeks. Ulceration may cause bleeding and this may be confused with further variceal haemorrhage.

Not surprisingly, it has been noticed that oesophageal function is abnormal following chronic injection sclerotherapy. Reilly and colleagues found abnormal

peristalsis in 12 of 13 patients following sclerotherapy (195). Although heartburn and retrosternal pain are common, minor complications immediately after sclerotherapy few patients complain of persistent oesophageal symptoms.

Despite the impression from uncontrolled reports that injection sclerotherapy is a much less hazardous treatment than the various surgical approaches to prevention of rebleeding from varices, and should therefore be preferable in less fit patients, one controlled trial has shown no statistically significant difference in survival between sclerotherapy and surgery. Cello and colleagues (196) randomised 52 patients who were Child's grade C and who had had bleeding from varices, to either chronic injection sclerotherapy or a portacaval shunt. 13 of 28 patients treated with sclerotherapy and 10 of 24 patients who had a portacaval shunt were discharged from hospital. Follow-up was for a mean of 263 days and at the time of reporting, nine patients in the sclerotherapy group and four patients in the shunt group were alive. Kaplan-Meir plots failed to show any significant difference in survival time. No controlled trial has compared chronic injection sclerotherapy with oesophageal transection.

Transhepatic obliteration of varices

In 1974 Lunderquist and Vang described a method of transhepatic obliteration of varices by embolisation of the coronary vein which had been cannulated by the transhepatic route (142). This was initially appealing as a further relatively non-invasive method of treatment. It could also be performed at the same time as diagnostic radiology and pressure measurements in the portal system.Over the ensuing years it became clear that there are two main drawbacks of this technique: firstly the need for highly specialised radiologists to perform it and secondly the complications associated with transhepatic cannulation of the portal vein. A comparison of transhepatic obliteration of varices with stapled oesophageal transection in uncontrolled bleeding from varices showed that both methods were equally effective in stopping the bleeding and that hospital mortality was similar (143). Despite this the need for specialised radiology has made transhepatic obliteration of varices an uncommon procedure.

The use of drugs in the prevention of rebleeding

The search for a drug which would lower portal pressure on a long term basis and thus prevent rebleeding from oesophageal varices has been widespread. In 1980 Lebrec and colleagues reported that propranolol caused a significant drop in portal pressure in sixteen cirrhotic patients who had had recent variceal bleeds (106) and propranolol was suggested as a medical treatment for portal hypertension. A further report from this group in 1981 (197) stated that the use of oral propranolol significantly reduced the number of bleeding episodes in patients with oesophageal varices. In 1984 they reported again on this trial and were able to show an improvement in two year survival in the group of patients treated with propranolol compared to the placebo treated group (198). However, initial enthusiasm has been dampened by the results of two subsequent trials which could demonstrate no reduction in rebleeding rates or improvement in survival (199,54). One of the most recent double blind, controlled trials of propranolol versus placebo has demonstrated only a small difference in late rebleeding rate and long-term survival, suggesting that propranolol is unlikely to be of value during the high risk period soon after a variceal bleed (200). The results of these trials are summarised in Table 1. It is generally felt that the excellent results obtained by Lebrec were due to a group of patients with significantly less severe liver disease than

most patients with varices and that propranolol has not been proven to be of use in the majority of patients. Lebrec's group have published work which confirms this reasoning, showing that the effect of propranolol on azygous blood flow is highly variable in Child's grade C patients (201). Lebrec's trial also included all causes of upper gastrointestinal haemorrhage in his varices patients, rather than only variceal bleeds and if recent reports of propranolol's efficacy in severe gastritis in portal hypertensive patients are confirmed (202), this may be another reason for Lebrec's good results.

Various other adrenoreceptor blockers have been assessed experimentally with regard to their portal pressure effects. Atenolol was found to reduce portal pressure less effectively than propranolol and prazozin had significant side-effects although portal pressure was reduced to the same extent as by propranolol (109). A new selective B2 blocker (ICI 118,551) has been studied in animals (203) and is thought to hold some promise, since a significant fall in portal pressure was demonstrated with no effect on heart rate or systemic blood pressure.

Cimetidine has also been studied with regard to prevention of variceal bleeding. Burroughs and colleagues were unable to show any effect on portal pressure in cirrhosis with cimetidine (110) and a controlled trial failed to show any difference between patients on regular cimetidine and those on placebo in terms of rebleeding from their varices (43).

There is therefore some debate about the place of long-term drug therapy in the prevention of variceal bleeding.

Table 1 - Results from four trials of the use of propranolol in the prevention of variceal haemorrhage.

AUTHOR	Lebrec (198)	Burroughs (199)	Villeneuve (54)	Garden (200)
n	56*	48	79	81
NUMBER REBLEEDING				
PLACEBO	17/28	11/22	30/37	33/43
PROPRANOLOL	2/28	12/26	32/42	19/38

*Only patients bleeding from varices are included here.

PROPHYLAXIS

The ultimate in prevention of bleeding from varices must be to prevent the first bleed, which carries a mortality of 25-50%. In the hey-day of shunt surgery in the United States prophylactic portocaval shunts were advised. However several controlled trials showed that survival was not improved and that morbidity due to encephalopathy and hepatic failure was unacceptable (204,205). Prophylactic shunts have therefore fallen out of favour.

Prophylactic sclerotherapy has been supported by Paquet (206) whose study published in 1982 showed a reduction in bleeding and mortality rate in patients with large varices. Only patients thought to be at high risk of bleeding were entered into this study and the bleeding rate in the control group was very high. Prophylactic sclerotherapy has not been widely accepted although it does seem much more likely to be a safe and useful undertaking than prophylactic shunt surgery.

Two multicentre studies have looked at the use of propranolol on a prophylactic basis. A French study reported significantly fewer bleeds (3% versus 26%) and deaths (3% versus 37%) over a twelve month follow-up period in subjects taking propranolol compared with the placebo group (207). An Italian study also showed less bleeding on propranolol but only when those who stopped taking the drug because of side-effects were excluded (208). The compliance factor is

obviously of great importance in studies of prophylaxis in a group of patients who are not always the best motivated.

The question of prophylaxis against the first variceal bleed therefore remains an open one. Further studies of both injection sclerotherapy and drug treatment are necessary.

AIMS OF THESIS

1. To assess the previous results of oesophageal tamponade as used in the University Department of Surgery, Glasgow Royal Infirmary, for acute variceal bleeding.

2. To study the acute effects of SMS 201-995 on systemic and portal haemodynamics in stable cirrhotic patients.

3. To examine the mode of action of SMS 201-995 using a radioactive microsphere method to measure cardiac output, organ blood flow and portasystemic shunting in normal rats, rats with extrahepatic portal hypertension and cirrhotic rats.

4. To compare the efficacy of SMS 201-995 with that of oesophageal tamponade in patients with active variceal bleeding.

CHAPTER 2

OESOPHAGEAL TAMPONADE IN THE MANAGEMENT OF VARICEAL HAEMORRHAGE

INTRODUCTION

As discussed in Chapter 1, for some years the mainstays of treatment for active variceal bleeding have been vasopressin and oesophageal tamponade. In the University Department of Surgery, Glasgow Royal Infirmary, oesophageal tamponade using the 4-lumen Minnesota modification of the Sengstaken-Blakemore tube has been the principal means of control of variceal bleeding for the past seven years. As a basis for future studies in control of variceal bleeding, the results of the use of oesophageal tamponade over this period have been reviewed, to assess not only the bleeding control rate, but also the problems associated with oesophageal tamponade.

PATIENTS AND METHODS

One hundred and thirty eight patients presented on 223 occasions to the University Department of Surgery, Glasgow Royal Infirmary from August 1979 until April 1986, with endoscopically proven bleeding oesophageal varices. Only patients who had bled within 24 hours of presentation are included in this review. Patients presenting with suspected variceal haemorrhage were initially resuscitated with a combination of crystalloid and colloid, and crossmatched blood where appropriate. At the time of admission, blood was taken for estimation of serum urea and electrolyte concentrations, full blood count and coagulation screen. Any coagulopathy was corrected by the administration of fresh frozen plasma and/or cryoprecipitate as appropriate. Vitamin K_1 (10mg daily) and cimetidine (400mg twice daily) were given parenterally to all patients. No patients in this series routinely received vasopressin or any other vaso-active agent to arrest their haemorrhage.

Early endoscopy was performed as part of the initial assessment of each patient. If active variceal haemorrhage was demonstrated at endoscopy and deemed to be so severe that it was unlikely to cease without intervention, tamponade was instituted using the Minnesota four lumen modification of the Sengstaken-Blakemore tube (81) If such proven haemorrhage was minimal and thought likely to cease without intervention, tamponade was not instituted until it was clear that bleeding was continuing i.e. further overt

haematemesis or occult haemorrhage reflected in a rising pulse rate and/or falling blood pressure. The tube was inserted by medical staff trained in its use. The initial practice was to pass the tube orogastrically, but in the last two years the nasogastric route was preferred. Nasogastric intubation has been found to be easier than orogastric intubation and was more acceptable to most patients who had experienced previous orogastric intubation. The gastric balloon was inflated with 100ml of water and 20ml of sodium meglumine iodamide (Uromiro 340, Merck Ltd). The oesophageal balloon was inflated with air to a pressure of 40mmHg as measured by an aneroid barometer. The position of the tube was confirmed by abdominal radiography immediately after insertion and the patient was constantly supervised by trained nursing staff in the University Department of Surgery ward. Open drainage of the gastric and pharyngeal channels of the Minnesota tube was supplemented by hourly syringe aspiration. Tube position was maintained simply by taping the tube to the side of the nose or to a spatula at the side of the mouth. Lactulose (15-30mls three times daily) was given enterally to minimise or avoid encephalopathy, and the rectum was irrigated through a rubber tube with up to eight litres of water or until a clear return was obtained. Sedatives and analgesics were avoided whenever possible.

The Minnesota tube was kept in position with both balloons inflated for 24 hours. The oesophageal balloon was then

deflated and the tube left in place for up to twelve hours. If bleeding did not recur then the tube was removed and destroyed to prevent reusage. If bleeding recurred the balloons were re-inflated. When the condition of the patient permitted, injection sclerotherapy using a modified Negus rigid oesophagoscope (209) was undertaken.

Recurrent variceal haemoorhage during admission was defined as the development of shock (pulse>100/min and/or systolic blood pressure<100mmHg) requiring continued resuscitation or the aspiration of fresh blood through the tube. Any such haemorrhage occurring after initial bleeding had ceased or been controlled with tamponade for 24 hours was deemed to be recurrent. Such recurrent bleeding was treated in a similar manner by tamponade.

The severity of the underlying liver disease was assessed in each patient using Pugh's modification of Chlid's grading (58). In addition a prognostic score was calculated on admission for each patient using the derived equation described by Garden et al (72). In that study three factors, namely prothrombin ratio, serum creatinine and the presence of encephalopathy, were found to have independent significance in the prediction of outcome, which, when taken together, accurately predicted outcome in 90% of cases.

To try to establish the aetiology of the portal hypertension, a liver biopsy was performed on all patients during initial or subsequent admissions, unless contraindicated by major coagulopathy.

RESULTS

One hundred and thirty eight patients were admitted on 223 occasions with endoscopically proven variceal haemorrhage. There were 93 males and 45 females with an average age of 53.3 years (range 17-82 years). The aetiology of the portal hypertension in these patients is shown in Table 2. Figure 1 illustrates the outcome of these 223 episodes of variceal haemorrhage.

Spontaneous cessation of haemorrhage

In 92 bleeds (41%) haemorrhage ceased without passage of the Minnesota tube. In only two did bleeding recur during admission (both after sclerotherapy) and in both cases tamponade controlled haemorrhage. Eight of the patients in this group died after bleeding had settled; seven of progressive liver failure and one following a cardiac arrest; six of these patients had sclerotherapy.

Failed intubation

Five patients would not tolerate insertion of the Minnesota tube. One patient, having experienced oesophageal intubations on six previous occasions, would not allow the tube to be passed on a seventh occasion. Vasopressin infusion failed to control haemorrhage and emergency sclerotherapy was required. Despite the eventual successful control of bleeding, the patient died of pneumonia three days later. In the youngest patient in our series, emergency oesophageal transection was required to arrest haemorrhage

when the tube was pulled up three times in quick succession before the balloons could be inflated. In one of the remaining three patients haemorrhage settled, but he died of hepatic failure. In a further patient haemorrhage initially settled but recurred and was controlled by tamponade, which was tolerated on the second occasion. He subsequently underwent sclerotherapy and this controlled bleeding.

Haemorrhage requiring intubation

Oesophageal tamponade was required for the remaining 126 bleeds (57%) and haemorrhage was initially controlled on 123 occasions (98%). Bleeding recurred on 44 occasions (35%) during these 123 admissions: 25 on deflation of the balloons and 19 following sclerotherapy. Oesophageal tamponade was required on all of the 47 occasions where bleeding recurred during admission (44 after tamponade, two where bleeding initially ceased and one where intubation was initially refused). Haemorrhage was controlled on 41 of these occasions (87%). A second episode of recurrent haemorrhage occurred on 11 occasions (two after sclerotherapy), tamponade was required on all 11 occasions and bleeding arrested on nine. Two patients rebled a third time (one after sclerotherapy) but in both patients haemorrhage was successfully controlled by tamponade. No patient rebled for a fourth time during one admission.

Overall, tamponade was successful in controlling variceal haemorrhage on 175 of the 186 occasions where its use was thought to be necessary (94%). It was more successful in

controlling haemorrhage in patients at initial presentation and in patients with less severe liver dysfunction as judged by modified Child's grade (Table 3).

Failed control of haemorrhage

The Minnesota tube failed to control variceal haemorrhage on ten occasions in nine modified Child's C grade patients and once in a modified Child's B grade patient. In the grade B patient haemorrhage was not controlled by re-intubation after the initial tube was pulled up by the patient. He subsequently required emergency oesophageal transection which controlled haemorrhage. Five of the modified Child's C grade patients died before any other life saving measure could be instituted and in two of these post-mortem examination revealed oesophageal tears thought to be caused by intubation. One further patient required emergency injection sclerotherapy which successfully controlled haemorrhage initially, but the patient rebled and died when intubation again failed to control haemorrhage. One patient pulled up the tube with balloons inflated before haemorrhage ceased and sustained a fatal cardiopulmonary arrest when the tube was repassed. In one patient repeat endoscopy demonstrated a bleeding gastric varix, which was successfully underrun at operation. The last of the nine modified Child's C patients bled after injection sclerotherapy and subsequent intubation failed to control bleeding. Haemorrhage gradually settled after it was decided that the patient was not fit for any active intervention,

and he died three days later of a chest infection.

Complications of tamponade

There were 28 complications attributed to oesophageal intubation in 186 episodes where tamponade was necessary (Table 4). Thirteen patients developed chest infections (defined as the development of a pyrexia, in the presence of abnormal physical or radiological signs in the chest and the absence of other obvious causes for the pyrexia, or the production of purulent sputum) but nine of them had undergone injection sclerotherapy under general anaesthesia following tamponade and prior to developing the infection. Seven of these patients died as a consequence of the infection.

Eight patients pulled up the tube with the balloons fully inflated. Most of these patients complained of transient dysphagia but one died from massive uncontrollable haemorrhage from an oesophageal tear which was confirmed at post-mortem. Four patients sustained a cardio-respiratory arrest on passage of the Minnesota tube: three were successfully resuscitated but one of these patients died (mentioned in the previous paragraph). There were no complications associated with the passage of the tube by the nasogastric route. In one patient the tube could not be passed due to nasal septal deviation but orogastric intubation was successful.

Deaths

Table 5 shows details of the deaths which were attributed

to oesophageal tamponade in relationship to whether sclerotherapy was undertaken during the final admission and in relation to the patient's calculated prognostic index (72). Four deaths were due to the failure of the tube to control haemorrhage. A further four deaths were definitely associated with the use of oesophageal tamponade. Seven deaths were due to chest infection. Four of these patients had sclerotherapy under general anaesthesia as well as oesophageal tamponade. One patient's death was completely unexplained. She had a cardio-respiratory arrest and could not be resuscitated. Post mortem examination showed no abnormality to explain this.

Table 2 - Aetiology of portal hypertension in 138 patients admitted with acute variceal haemorrhage and its relationship to Child's grade.

	CHILD'S GRADE			
	A	B	C	Total
Alcoholic cirrhosis	4	21	73	98
Chronic active hepatitis	1	5	6	12
Cryptogenic cirrhosis	0	8	1	9
Primary biliary cirrhosis	-	2	4	6
Portal vein thrombosis	2	2	-	4
Primary sclerosing cholangitis	1	-	1	2
Idiopathic portal hypertension	-	1	1	2
Metastatic breast carcinoma	-	-	1	1
Pancreatic carcinoma	-	1	-	1
Wilson's disease	-	1	-	1
Unknown	-	2	-	2
TOTAL	8	43	87	138

Table 3 - Control of haemorrhage by tamponade and its relation to modified Child's grade.

	CHILD'S GRADE		
	A	B	C
Initial bleeds	n=4	n=42	n=80
no of patients in whom initial bleed controlled	4(100%)	42(100%)	77(96%)
Rebleeds	n=2	n=17	n=41
no of patients in whom rebleed controlled	2(100%)	16(94%)	34(83%)

Table 4 - Complications of oesophageal tamponade. Figures in parenthesis denote deaths related to use of Minnesota tube.

	CHILD'S GRADE		
	A	B	C
Aspiration + chest infection (no sclerotherapy)	-	-	4(3)
Aspiration + chest infection (post-sclerotherapy)	-	4(1)	5(3)
Oesophageal tear on intubation	-	-	2(2)
Pulled up tube	1	2	5(1)
Cardiac arrest	-	1	3(1)
Unexplained death	-		(1)
TOTAL	1	7(1)	20(11)

Table 5 - Deaths thought to be associated with tamponade in relation to sclerotherapy and prognostic index.

PATIENT	AGE	SEX	CHILD'S GRADE	CAUSE OF DEATH	SCLEROTHERAPY	PROGNOSTIC INDEX
JMcG	61	M	C	failed control	+	0.00
PMcG	55	M	C	chest infection	-	0.00
PB	67	M	C	oesophageal tear	-	0.01
JK	39	F	C	failed control pulled up tube & arrested	-	0.03
HD	52	M	C	chest infection	+	0.06
RW	54	M	C	chestinfection	+	0.08
AR	46	M	C	oesophageal tear	-	0.11
TMcL	47	M	C	failed control	+	0.21
JD	56	M	C	failed control	-	0.21
DJ	66	M	B	chest infection	-	0.23
TA	68	M	C	failed control &chest infection	+	0.35
AB	36	M	C	failed control	+	0.38
MG	61	F	C	pulled up tube	+	0.66
MT	50	F	C	chest infection	-	0.84
HS	69	F	C	chest infection	+	0.87
MP	68	F	C	unexplained death	-	0.91

Patients with prognostic score >0.66 would have been expected to survive admission.

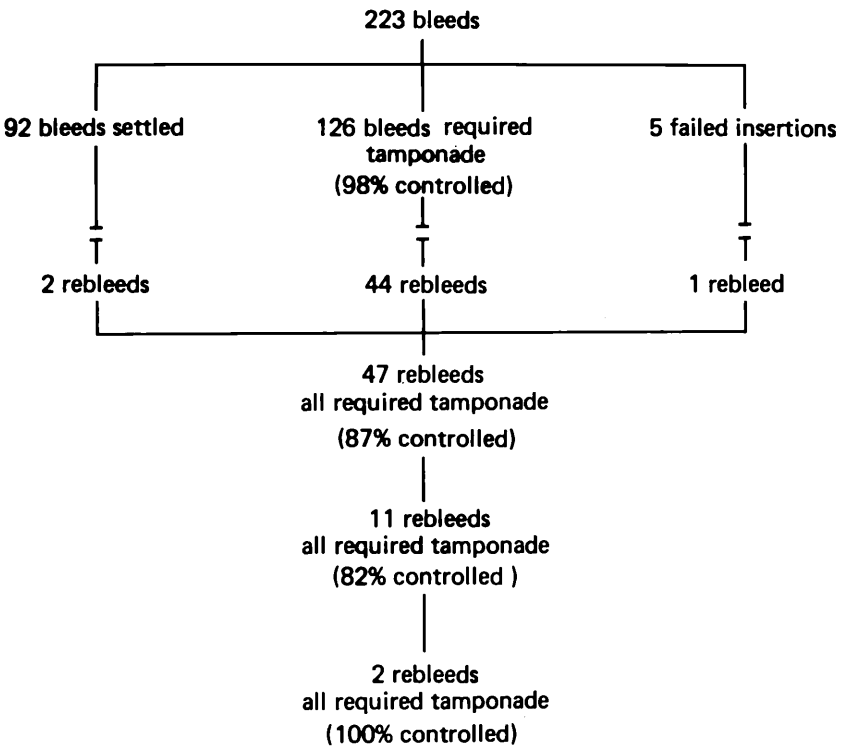

Figure 1 - Outcome of 223 initial episodes of acute variceal haemorrhage in 138 patients.

DISCUSSION

The use of oesophageal tamponade in the management of bleeding oesophageal varices became accepted after Sengstaken and Blakemore (79) described their double ballooned tube. However the problem of regurgitation of gastric contents and aspiration of oesophageal and gastric secretions was reported by several authors over the next few years (210,211). Because of this problem, Boyce (212) suggested the use of a plastic nasogastric tube taped to the 3-lumen tube for aspiration of the oesophagus and this led to the development of the Minnesota tube which incorporates all four lumens within one tube (81). Mitchell (213) has shown that this tube is less uncomfortable and associated with less respiratory complications than the 3-lumen tube.

The present study confirms that many patients referred with variceal haemorrhage will settle without active intervention to stop the bleeding. In this study 42% of all acute bleeds presenting to hospital settled without any active intervention, although on three occasions (two where intubation was not required and one where the patient refused intubation) further haemorrhage during admission required tamponade. This sub-group with spontaneously settling bleeds had a similar distribution of modified Child's grade to the group requiring tamponade. Variceal size was not recorded accurately enough for comparison between the groups. Endoscopy was undertaken in all patients to exclude other potential sites of blood loss since it has

been shown (67,69) that as many as 30% of patients known to have oesophageal varices are in fact bleeding from other sites. The observation that many patients with confirmed variceal bleeding settle without intervention, may help to explain the variable results obtained in studies of control of variceal haemorrhage, since there is considerable variation in the entry criteria to these studies. Some authors are happy to include all patients with haematemesis or melaena in the 24 hours prior to admission (214), while in other reports only patients who had been shocked (5), patients who had bled more than 1000ml (89) or patients who had failed to respond to conservative measures (168) are included.

The 94% control of variceal haemorrhage by tamponade seen in the present series is very similar to the 80-90% control rate reported by some other authors (69,83,215). This high control rate was achieved in a predominately poor risk group comprising 63% modified Child's C grade patients. Those patients in whom control of haemorrhage was not achieved all had poor prognostic scores (72), having advanced liver disease with marked coagulopathy. Table 6 summarises the results obtained with oesophageal tamponade by some other groups. Pitcher (83) performed a prospective study in 50 patients using the Boyce modification of the Sengstaken-Blakemore tube and obtained an 88% bleeding control rate. Bauer (215) reported an 80% initial control rate in 35 episodes of variceal bleeding in 25 patients.

More recently, Panes (1) has achieved a 91.5% control rate in 108 patients with bleeding oesophageal varices using the Sengstaken-Blakemore tube. On the other hand, Conn (82) found only a 56% bleeding control rate in 40 patients. Further examination of his report reveals that endoscopy to confirm the site of blood loss was not always performed and the possibility that a number of patients were bleeding from other lesions may help explain the poor control rate. Tamponade was also avoided until the patient had had a significant amount of blood transfused, presumably resulting in a deterioration in their coagulation status. In Conn's study, a 3-lumen tube was passed by house officers and was noted to be incorrectly used in 26% of cases. This contrasts with other studies (83,1), where experienced medical and nursing staff working in intensive care or specialised units have been involved in patient care. This factor undoubtedly contributed to the good control rate in the present study.

There is much controversy regarding the incidence of serious complications associated with tamponade (211,82,83,1). Conn and Simpson proposed that oesphageal tamponade should only be used as a last resort in controlling variceal haemorrhage because of the high complication rate seen in their centre, and that prophylactic tracheostomy or endotracheal intubation prior to the use of the tube should be seriously considered in an attempt to prevent these complications (82). They found that 14 of 40 patients (35%) admitted with acute variceal

haemorrhage treated with oesophageal tamponade suffered major complications; death was attributable to the use of the tube in 9 patients (22%). Pitcher (83), in contrast, reported a very low complication rate. The majority of the other reports have shown a complication rate of between 10 and 20% (Table 6) and this is consistent with our complication rate per bleed of 15%. The mortality per bleed attributed to tamponade in the present series was 6.4% (not including patients with failed control). Patients with a prognostic score of 0.66 or greater would have been expected to survive admission (72). It is interesting to note that in only four of the deaths associated with tamponade was the prognostic score of the patient greater than 0.66. It could be argued that factors other than tamponade contributed significantly to the deaths of the twelve patients with poor prognostic scores, although the possibility that the two patients who suffered oesophageal tears on intubation might have survived had this event not occurred cannot be ignored.

Aspiration of secretions is the most common complication of oesophageal tamponade (82,215,217). The policy in the University Department of Surgery, Glasgow Royal Infirmary has been to avoid sedation of patients when passing the tube to try to reduce the risk of aspiration pneumonia. However, intubation in restless patients may also be hazardous. The 10.3% incidence of pneumonia per intubation in the present series may reflect unfairly on oesophageal tamponade given that many of these patients proceeded to sclerotherapy under

general anaesthesia. The use of a 4-lumen tube should reduce the risk of this complication (213) and it may be that the use of endotracheal intubation in the limited group of patients with severe encephalopathy would reduce this risk in that group (1).

Rupture of the oesophagus can occur from inflation of the gastric balloon in the oesophagus (217), from perforation of the oesophagus by the tube itself (82) and following precipitous removal of the tube with balloons inflated (60). In the present series, the tube was removed by the patient with balloons inflated on eight occasions. Limited inflation of the gastric balloon may account for the fact that only one such patient sustained an oesophageal rupture.

Therefore, in the present study, oesophageal tamponade has been shown to provide good control of bleeding from oesophageal varices. However there is a significant complication rate and four deaths were certainly associated with the use of tamponade while in eight other deaths tamponade may well have been contributary. Patients experience marked discomfort due to oesophageal tamponade and this cannot be disregarded. In view of these findings, the search for an effective drug for the control of variceal haemorrhage is of considerable importance.

Table 6 - Summary of some results previously published describing the use of oesophageal tamponade in variceal bleeding.

AUTHOR	CONTROL RATE	COMPLICATION RATE	MORTALITY RATE
Read, 1960	84%	-	74%
Conn, 1967	56%	35%	22% (due to tube)
Novis, 1976	85%	30%	48%
Pitcher,1971	88%	4%	36%
Bauer, 1974	80%	9%	
Chojkier,1980	40%	16%	90%
Sarin, 1984	87%	15%	0%
Panes, 1988	92%	10%	33%

CHAPTER 3

THE ACUTE EFFECTS OF SMS 201-995 ON PORTAL AND SYSTEMIC HAEMODYNAMICS IN STABLE CIRRHOTIC PATIENTS.

INTRODUCTION

Before SMS 201-995 can be considered for use in acute variceal bleeding it is essential to establish its effect on portal pressure in stable portal hypertensive patients. There are two publications on this subject in the literature. One is an abstract in which Burroughs and colleagues report that SMS 201-995 had no effect on portal pressure (137). However in this work a variety of doses given as intravenous boluses or infusions was given to only six cirrhotic patients and no controls were used. The second publication is from Wahren and Eriksson in Scandinavia (138) and shows a reduction in hepatic blood flow and wedged hepatic venous pressure in nine cirrhotics given a varying dose of SMS 201-995. Cardiac outputs were not measured in either of these studies. In the present study the effects of a 25μg/hr intravenous infusion of SMS 201-995 on both systemic and portal haemodynamics have been studied in stable cirrhotic patients.

PATIENTS AND METHODS

The study group comprised sixteen patients with histologically proven hepatic cirrhosis who had had an endoscopically proven bleed from oesophageal varices. All patients were aged between 18 and 70 years and had been haemodynamically stable for at least seven days prior to the study. Patients with a history of cardiac disease, diabetes mellitus or renal disease and those taking vasoactive drugs were excluded. All patients gave written informed consent and the study was approved by the Ethical Committee of Glasgow Royal Infirmary.

The patients were admitted to hospital on the day prior to the study and were assessed by full physical examination, urinalysis (Multistix, Ames) and measurement of full blood count, coagulation screen (prothrombin time, kaolin cephalin coagulation time, thrombin time and platelet count), serum urea and electrolyte concentrations, liver function tests (bilirubin, alkaline phosphatase, alanine and asparate transaminases) and serum protein and albumin, gamma glutamyl-transferase and cholesterol levels. This enabled the allocation of each patient to a modified Child's grade as described by Pugh (58). Height and weight were recorded. Body surface area was estimated using a nomogram based on the formula

body surface area =

$$0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}.$$

Chest X-ray and 12 lead electrocardiograph were performed.

Right heart catheterisation was then performed under fluoroscopic control using a ballon-tipped thermodilution Swan-Ganz catheter (RMS,93A-131-7F) introduced via the right femoral vein by the Seldinger technique (218). The zero reference point was taken at the mid-axillary line. Measurements were made of right atrial, pulmonary arterial and pulmonary capillary wedge pressure by attaching the fluid filled catheter to an external pressure transducer (Statham strain gauge and Gould transducer amplifier 13-465-50). Left ventricular filling pressure was taken as pulmonary artery diastolic pressure if this was within 2mm Hg of the pulmonary capillary wedge pressure. Systemic blood pressure was measured with a cuff on the left arm using a standard mercury sphygomanometer.

Cardiac output was estimated by the thermodilution method (22) using an American Edwards Laboratories COM-1 cardiac output computer. Immediately following these systemic haemodynamic measurements the catheter tip was manipulated into the hepatic vein where measurements of wedged hepatic vein pressure and free hepatic vein pressure were made. Fluoroscopy was used to confirm the catheter position and a typical venous pressure wave was always obtained before measurements were performed. All pressure measurements were transferred onto hard copy using an ink-jet recorder (Siemens Mingograff) with a paper speed of 50mm/s.

These measurements were made at 0 minutes, 60 minutes, 120 minutes and 180 minutes. Nine patients received an

intravenous infusion of 25ug SMS 201-995 in 125ml of normal saline between zero and 60 minutes. Seven patients acted as controls and were given no SMS 201-995. In the patients given SMS 201-995 blood was sampled from the right atrium via the catheter for estimation of drug levels at -15, 5, 15, 30, 45, 60, 90, 120, 150 and 180 minutes. The catheter was removed after the final measurements and haemostasis ensured. At twenty-four hours the pre-investigation assessment was repeated.

Haemodynamic indices were calculated as follows:

1) Cardiac index ($l/min/m^2$) = cardiac output/ body surface area

2) Systemic vascular resistance ($dynes/s/cm^5$) =
(mean arterial pressure - mean right atrial pressure)
/cardiac output

3) Transhepatic venous gradient (mmHg)=
wedged hepatic venous pressure -
free hepatic venous pressure

SMS 201-995 levels in the patients receiving the drug were assayed using radioimmunoassay. RIA kits SMS 201-995 were supplied by Sandoz Horsforth. This radioimmunoassay has been developed using a polyclonal antiserum from rabbit (219). At the 95% confidence level detection is limited to 5pg/ml with

a 0.1ml aliquot of human blood plasma. Within assay and between assay variability at the 25pg/ml dose level has been found to be 5% and 10% respectively (219).

The data were analysed using repeated analysis of variance with the Greenhouse-Geisser correction to the degrees of freedom. The time courses in the two groups were compared by testing for a time by treatment interaction. The level of significance was chosen as the 5% level.

RESULTS

The two groups of patients were comparable in terms of age, aetiology of liver disease, and Pugh's modification of Child's grade (Table 7).

The results of the haemodynamic study are summarised in Table 8. The results for individual patients are shown in Appendices 1 and 2. Figures 2 and 3 show the changes in wedged hepatic venous pressure and transhepatic venous gradient with time in the two groups of patients.The groups differed with respect to the changes in wedged hepatic venous pressure ($p=0.036$) and transhepatic venous gradient ($p=0.032$). In the SMS 201-995 group mean wedged hepatic venous pressure fell by 22% and mean transhepatic venous gradient fell by 30% at 60 minutes. By 120 minutes these pressures had returned to values not significantly different from those recorded prior to SMS 201-995 infusion. In the control group there was no significant fall in wedged hepatic venous pressure and transhepatic venous gradient.

Figures 4 and 5 show the changes in cardiac index and systemic vascular resistance with time for the two groups of patients. There were no significant differences between the groups in terms of cardiac index and systemic vascular resistance, but in both groups there were significant changes in these variables with time ($p<0.01$). Cardiac index was reduced and systemic vascular resistance increased at 60 minutes despite there being no significant changes in heart rate or arterial blood pressure during the study

period.

No side-effects were experienced by the patients who received SMS 201-995 and there were no complications of the cardiac catheterisation. Electrocardiographs, chest X-rays and laboratory parameters were unchanged following the procedure.

Mean plasma SMS 201-995 levels in eight of the nine patients given the drug are shown in Figure 6. Very low levels of SMS 201-995 were found in the samples from one patient. Investigation revealed that there had been considerable delay in the preparation of the samples and this patient's results were therefore discarded.

Table 7 - The characteristics of the stable cirrhotic patients in the control and study groups

	CONTROL GROUP	SMS 201-995 GROUP
Number	7	9
Age (mean ± standard error)	57±3.0	52±2.0
Pugh's modification of Child's grade		
A	4	4
B	2	3
C	1	2
Aetiology of liver disease		
Alcoholic cirrhosis	6	7
Primary biliary cirrhosis	1	0
Chronic active hepatitis	0	1
Sclerosing cholangitis	0	1

Table 8 - Portal and systemic haemodynamic results in control and study groups at 0, 60, 120 and 180 minutes from the start of a 60 minute infusion of saline or SMS 201-995. Cardiac index (CI) is shown in $l/min/m^2$, systemic vascular resistance (SVR) in $dynes/s/cm^5$, wedged hepatic venous pressure (WHVP) in mm Hg and transhepatic venous gradient (THVG) in mm Hg. Results are shown as mean ± standard error of the mean.

SMS 201-995 GROUP	0	60	120	180
CI	4.9±0.42	4.3±0.42	4.3±0.38	4.4±0.4
SVR	820±83	950±89	892±87	935±103
WHVP	18.9±1.5	14.7±1.3	18.5±2.0	19.1+2.0
THVG	14.1±1.7	9.9±1.4	14.7±2.0	14.5±2.0
CONTROL GROUP	0	60	120	180
CI	4.5±0.35	3.6±0.22	3.9±0.33	4.1±0.31
SVR	885±42	1073±69	981+75	959±81
WHVP	14.8±1.4	14.6±1.1	15.6±1.6	16.8±2.9
THVG	8.8±2.1	7.8±1.3	8.0±1.1	8.6±1.0

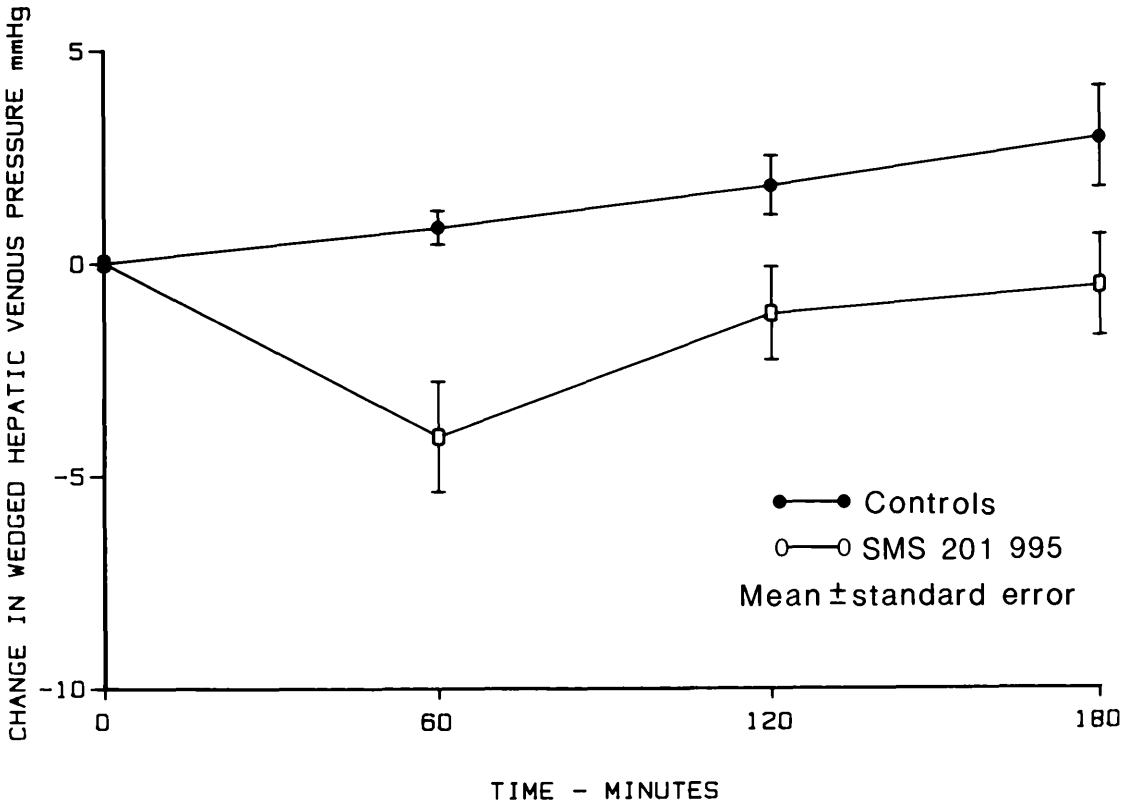

Figure 2 - The change in wedged hepatic venous pressure with time in two groups of cirrhotic patients. One group of nine patients given 25μg SMS 201-995 in 125ml normal saline as an intravenous infusion over 1 hour. Control group of seven patients given no drug.

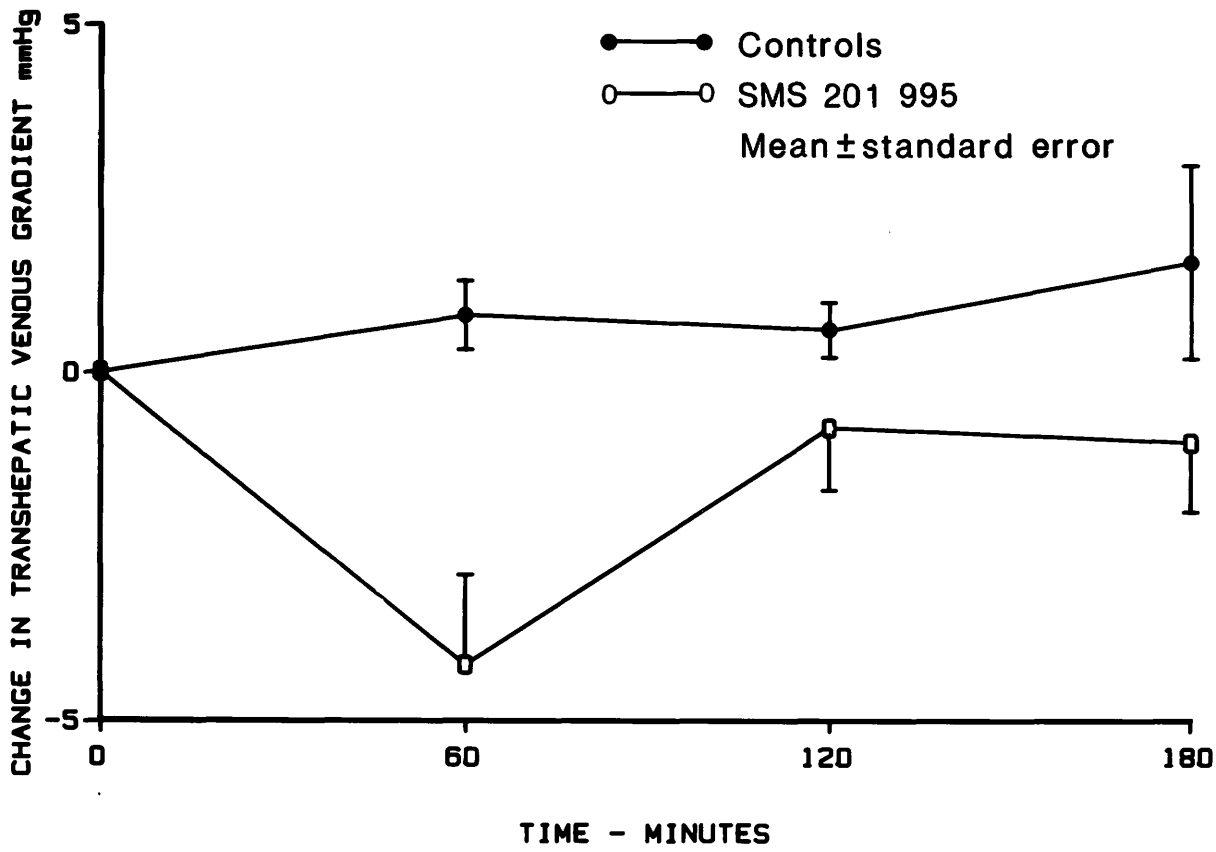

Figure 3 - The change in transhepatic venous gradient with time in two groups of cirrhotic patients. One group of nine patients given 25μg SMS 201-995 in 125ml normal saline as an intravenous infusion over 1 hour. Control group of seven patients given no drug.

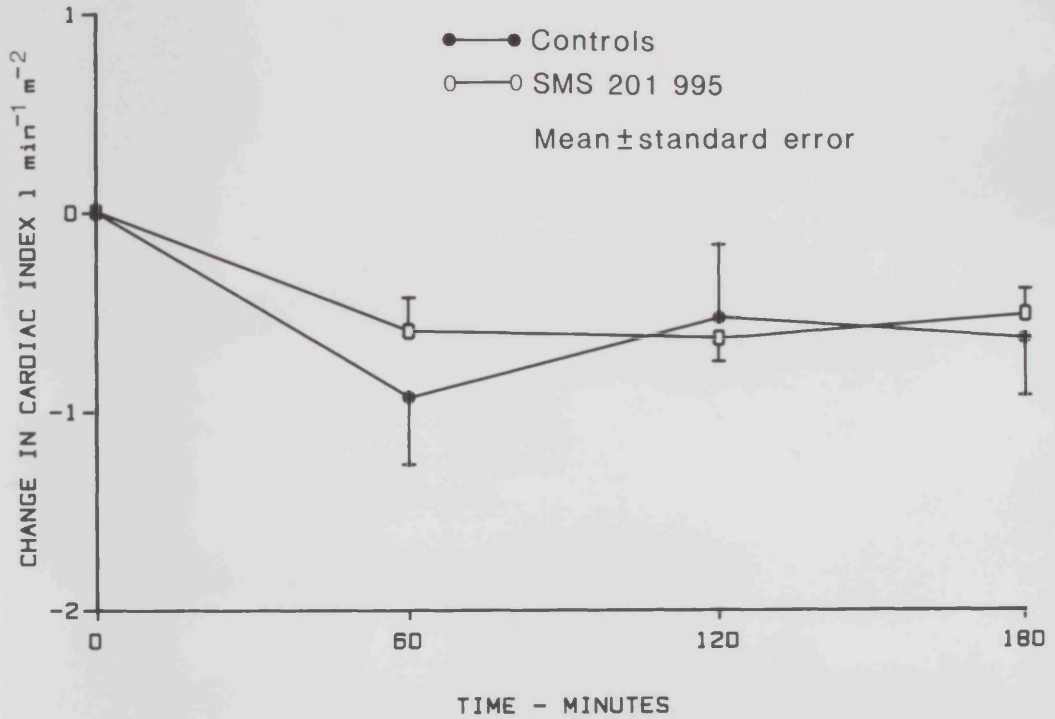

Figure 4 - The change in cardiac index with time in two groups of cirrhotic patients. One group of nine patients given 25µg SMS 201-995 in 125ml normal saline as an intravenous infusion over 1 hour. Control group of seven patients given no drug.

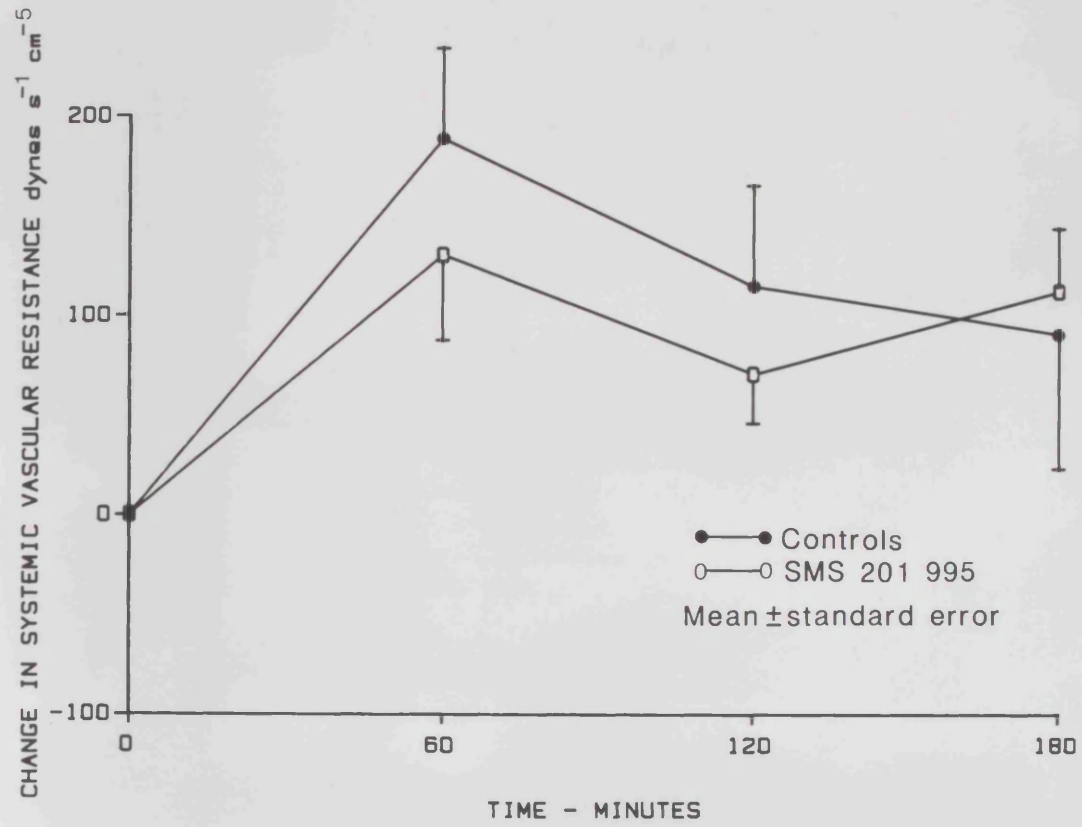

Figure 5 - The change in systemic vascular resistance with time in two groups of cirrhotic patients. One group of nine patients given 25µg SMS 201-995 in 125ml normal saline as an intravenous infusion over 1 hour. Control group of seven patients given no drug.

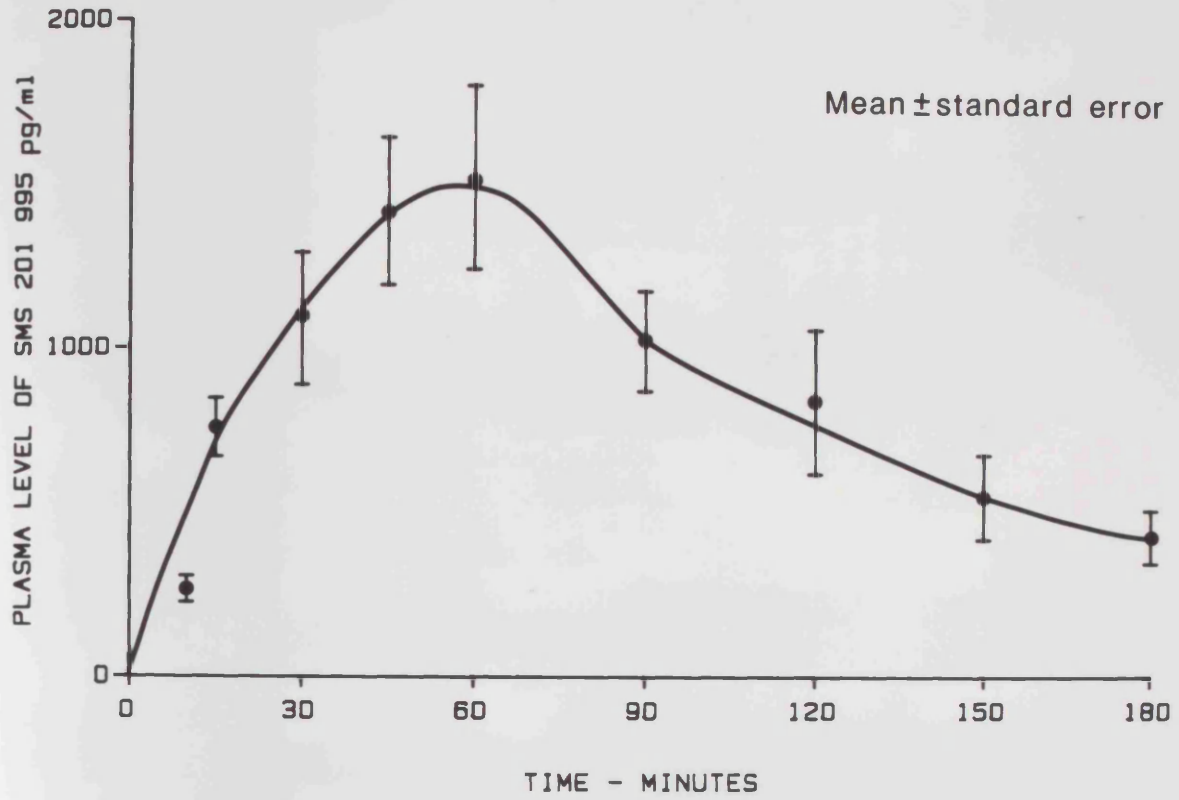

Figure 6 - Mean plasma levels of SMS 201-995 with time for eight of nine patients given an intravenous infusion of 25 µg SMS 201-995 in 125ml normal saline between 0 and 60 minutes.

DISCUSSION

This study has demonstrated that intravenous infusion of SMS 201-995 results in a significant reduction in portal pressure in patients with cirrhosis of the liver. One previous study was unable to demonstrate any effect on portal pressure in cirrhotics but only six patients were studied and no consistent dose of SMS 201-995 was used (137). Another study by Wahren's group (138) demonstrated a 25-35% reduction in hepatic blood flow as measured by indocyanine green in nine cirrhotic patients as well as a significant reduction in wedged hepatic venous pressure from 18±2 mmHg to 15±2 mmHg (mean±standard error). However in neither of these studies were systemic haemodynamics examined in detail and neither study used a control group of cirrhotic patients who did not receive SMS 201-995.

In the present study a 25μg/hr infusion of SMS 201-995 was used since this was considered likely to have a haemodynamic effect equivalent to that of a 250μg/hr infusion of naturally occurring somatostatin. An intravenous infusion was used because it is likely to be the method used in the treatment of acute variceal bleeding if the drug is of clinical value. The drug levels achieved were consistent with a 45 minute half-life.

Transhepatic venous gradient was used as a measurement of portal pressure in our largely alcoholic group of patients. In alcoholic liver disease it has been established that this measurement is comparable with direct measurement of portal

pressure using a thin needle (220,221). Repeated measurements of transhepatic venous gradient are possible, even in ascitic patients, whereas this is difficult and more dangerous using a thin needle to measure portal venous pressure directly.

Previous animal work (131) has suggested that SMS 201-995 may act by reducing splanchnic blood flow by pre-splanchnic arteriolar vasoconstriction. Splanchnic blood flow, measures approximately 1.5 l/min in man and is a significant part of cardiac output. It might therefore be expected that splanchnic vasoconstriction would cause an increase in total systemic vascular resistance. There are several potential reasons why we have not demonstrated this. Firstly, the increase in systemic vascular resistance may not be large enough to show as a significant change in our patients with their fairly large range of systemic vascular resistance (514-1189 dynes/s/cm).Secondly, it is possible that SMS 201-995 causes vasodilatation in other vascular beds which compensates for splanchnic vasoconstriction. Thirdly, the animal work suggesting pre-splanchnic vasoconstriction as a mechanism of action for SMS 201-995 takes no account of the effect of portasystemic shunting of blood and the effects of SMS 201-995 on the percentage porta-systemic shunting in man is unknown.

Although there are no statistically significant changes in the wedged hepatic venous pressure and transhepatic venous gradient in the control patients it will be noted that this

group had lower portal pressures at time zero than the group receiving SMS 201-995. However, the control patients showed no drop in portal pressure throughout the study period in comparison to a reduction of 30% in transhepatic venous gradient in the group receiving SMS 201-995. All patients in the latter group sustained a fall in transhepatic venous gradient at 60 minutes.

Investigations of the systemic haemodynamics demonstrated a high mean resting cardiac index and a low mean systemic vascular resistance. This haemodynamic profile is a common finding in patients with cirrhosis (222) and may be the result of several mechanisms including arteriovenous shunting of blood, increased catecholeamines (223) and a reduction in the degradation of circulating vasoactive metabolites (224).

During the study period there was an initial significant reduction in cardiac index and increase in systemic vascular resistance in both groups. The inclusion of a control group with cirrhosis allowed us to separate the effects of the infusion from the effects of bed rest itself. The change in these haemodynamic indices was of similar magnitude in both groups and therefore not attributable to SMS 201-995. Without a control group an erroneous assumption of the systemic effects of SMS 201-995 would have been made and therefore the results of studies without matched controls should be interpreted with caution. It remains to be determined why the cardiac index should fall with bed rest

in patients with cirrhosis, exactly the opposite from the response in severe heart failure (225). This phenomenon has been noted previously by Lebrec's group (226). It may be that bed rest transiently reverses the haemodynamic consequences of cirrhosis allowing the cardiac index to return towards normal.

In this study SMS 201-995 has been shown to have a significant effect on portal haemodynamics with no significant effect on systemic haemodynamics. No side-effects were experienced. The natural hormone, somatostatin, has been used to control upper gastrointestinal bleeding (117) and bleeding from oesophageal varices (118). In a randomised study in 63 patients, Kravetz and colleagues (4) reported that 53% of variceal bleeds were completely controlled by somatostatin in comparison to 58% controlled by vasopressin. Jenkins and colleagues (5) found that somatostatin controlled ten of ten variceal bleeds in comparison with four of twelve variceal bleeds controlled with vasopressin. These results were achieved with no major complications in patients receiving somatostatin. However the very short half-life of somatostatin limits its clinical use since any disturbance of the intravenous infusion will rapidly reduce the effects of the drug. This may help explain the different results of the two clinical studies of somatostatin in variceal haemorrhage (4,5). With a half-life of 45 minutes in plasma, a proven effect on portal pressure and no major

side-effects, SMS 201-995 could prove more useful in the practical management of bleeding oesophageal varices.

CHAPTER 4

RAT MODELS OF EXTRAHEPATIC AND INTRAHEPATIC PORTAL HYPERTENSION

INTRODUCTION

In order to study the effects of SMS 201-995 in more detail, an animal model of portal hypertension is necessary. Results of portal vein ligation experiments in both the dog (227) and the monkey (228) have been unsatisfactory as collateral vessels rapidly develop which are sufficient to decompress the portal venous system. Fortunately partial portal vein ligation in the rat has proved a better model and this has been used in the work for this thesis as a model of extrahepatic portal hypertension.

However the majority of patients suffer from portal hypertension secondary to chronic liver disease and not only have an increased portal pressure but have abnormal liver function. A model of intrahepatic portal hypertension would therefore be helpful in further assessing drug effects. The liver has an unpredictable response to toxins and some difficulty has been experienced in developing an adequate animal model of cirrhosis. For instance, repeated doses of alcohol over four years in baboons resulted in cirrhosis in only two of thirteen animals studied (229). In recent years carbon tetrachloride has been the most widely used hepatotoxin and in this thesis repeated doses of carbon tetrachloride have been used to produce cirrhosis in rats.

ANIMALS AND MAINTENANCE

Male Sprague Dawley rats (Bantin and Kingman Limited, Hull) were used in all animal experiments. They were housed in stainless steel cages with a maximum of six rats per cage. The animal house had an automated twelve hour light/dark cycle and air conditioning with a relative humidity of 50±5% and a temperature range of 21±1 C. Animals were fed on a standard rat diet (RN1(E) rat chow, Special diet services Ltd, Witham, Essex) with water ad libitum.

RAT MODELS

partial portal vein ligation

In 1979 Halvorsen and Myking (230) described and characterised a rat model of extrahepatic portal hypertension, in which a calibrated stenosis of the portal vein was produced by partial portal vein ligation. They had previously reported that a stenosis of 1.2mm diameter gave portal hypertension with a mortality of 25% (231). In the present study a similar method has been used to produce a rat model of extra-hepatic portal hypertension. The partial portal vein ligation was performed as follows. Rats were anaesthetised with halothane and a mixture of 2:1 nitrous oxide and oxygen. Laparotomy was performed via an upper midline incision. In the rat the portal vein is formed by the confluence of the superior mesenteric vein and the splenic vein and the pyloric vein joins this vessel in the lesser omentum before the portal vein divides into left and right branches at the porta hepatis (Figure 7). A 21G needle (outer diameter 0.81mm) was placed alongside the mobilised portal vein and a calibrated stenosis created by placing a 3/0 silk tie around the needle and the portal vein, cranial to the pyloric vein. The needle was then removed, the abdomen closed with two layers of chromic catgut and the rat allowed to recover. There is a 25% mortality from this procedure, resulting from tears to the portal vein, portal vein thrombosis and accidental ligation of the hepatic artery. Figure 8 is a portogram illustrating the anatomy of

this procedure, taken two hours after partial portal vein ligation had been performed.

Previous studies in this department have characterised this model (7). Partial portal vein ligation was performed as described above and portal pressure and %portasystemic shunting measured in groups of 6 portal vein ligated rats and 6 sham operated rats at days 1 to 10 and days 14, 21 and 28. Portal pressure was measured by cannulation of the ileo-colic tributary of the portal vein and %portasystemic shunting by the injection of radioactive microspheres into this portal vein cannula. These methods will be described in full later. At three days post-ligation portal vein pressure was shown to be three times that in sham operated controls and portasystemic shunting 37.4$\pm$17.2% (7). By twenty-eight days post-ligation portal vein pressure is 1.5 times that in sham operated controls and portasystemic shunting was 50.7$\pm$26.7% (7). Liver function tests and liver histology were normal throughout. This therefore provides a model of extrahepatic portal hypertension.

ANATOMY
OF PORTAL VENOUS SYSTEM OF THE RAT

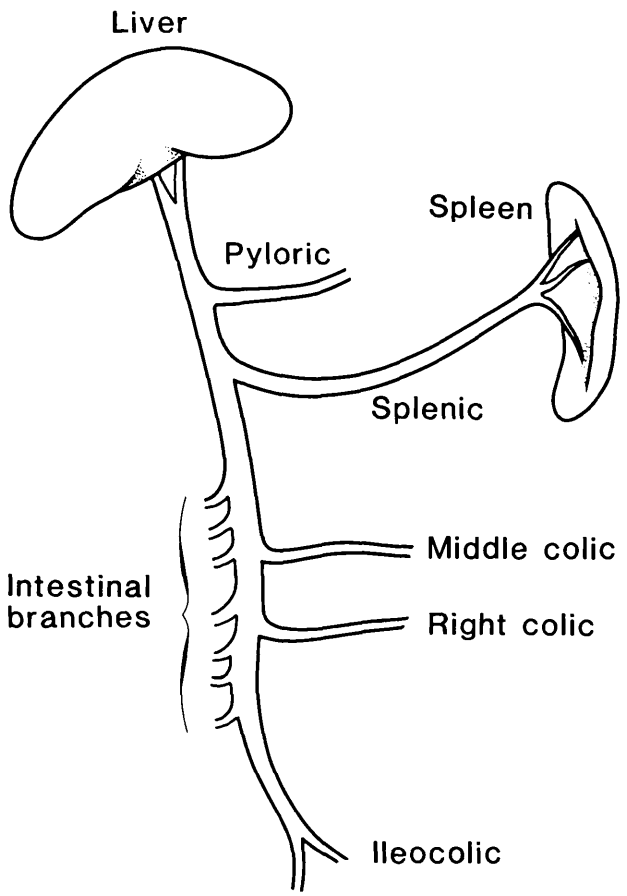

Figure 7 - The anatomy of the portal venous system in the rat. Partial portal vein ligation was performed by graded ligation of the portal vein cranial to the entry of the pyloric vein. Cannulas to measure portal pressure were inserted into the ileo-colic vein and threaded cranially to a level just below the junction of the splenic and superior mesenteric veins.

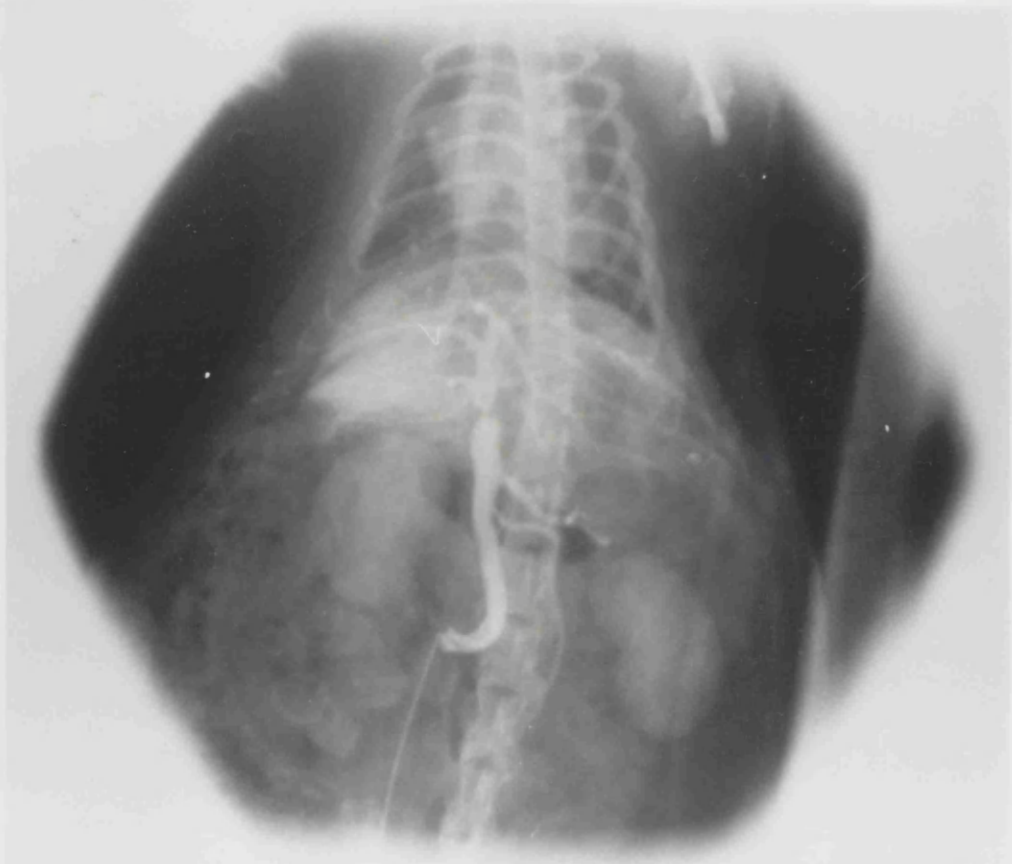

Figure 8 - Portogram showing the anatomy of partial portal vein ligation in the rat. Portogram performed two hours after portal vein ligation by injecting 5ml of Urograffin 90 into a cannula just inserted into a tributary of the ileo-colic vein. X-ray exposure time 0.05 seconds, penetration 60kV, distance of 40cm from rat (Siemens image intensifier).

Carbon tetrachloride induced cirrhosis.

The production of a small animal model of hepatic cirrhosis has been difficult because of the unpredictable hepatocellular reponse to toxins. Carbon tetrachloride has been the most widely used toxin in recent years but is not without problems. There is significant variation in response between animals and a reduction in sensitivity to carbon tetrachloride with age. However Procter and Chatamra (232) developed a method of production of cirrhosis using weight loss as an index of the sensitivity of each animal to carbon tetrachloride. This method has been used to induce cirrhosis in rats.

Animals weighing approximately 150g were used. Phenobarbitone (BDH Chemicals Ltd, Poole) was added to their drinking water (50mg/100mls) to activate the enzyme cytochrome P450 which has been shown to increase both liver size (233) and its sensitivity to carbon tetrachloride (234). After ten days of phenobarbitone treatment, gavage with carbon tetrachloride was commenced. Carbon tetrachloride (BDH Chemicals Ltd, Poole) was given by gavage via a specially designed Portex tube (5FG) which allowed the toxin to be administered with a tested accuracy of 0.04mls. Gavage was performed under general anaesthesia with 4% halothane in a 2:1 nitrous oxide:oxygen mixture which was delivered to a perspex box at high flow rates (nitrous oxide 2l/min and oxygen 1l/min) to enable rapid induction. The initial dose of carbon tetrachloride is important as

cirrhotic yield depends on the initial damage to the rat hepatocytes (232). This initial dose, defined as half the dose at which deaths occur, had been established previously as 0.15ml (7). Subsequent weekly doses of carbon tetrachloride were determined by using the percentage weight loss following the preceding dose as an index of the degree of hepatocellular injury (232). Thus, if massive weight loss occurred a reduction of 50% in the next dose was necessary while little weight loss, or particularly weight gain, necessitated a doubling of the subsequent dose of carbon tetrachloride. Repeated damage to the liver sufficient to cause chemical hepatitis without resulting in acute liver failure (233) was therefore achieved by titrating the percentage weight loss from the preceding dose of carbon tetrachloride against the next dose. The recognition of the onset of ascites was important as a marked reduction in the amount of carbon tetrachloride given was necessary to avoid an increase in mortality. From the fourth week of gavage, each animal was held erect under anaesthesia before gavage and the presence of free fluid in the abdomen assessed by inspection and palpation of the lower abdomen. At the same time, splenic palpation was performed. Early ascites was sometimes difficult to detect on clinical examination alone, and a more sensitive index of subclinical ascites was a sudden rise in weight (20-30g) at day 3 or 4 after gavage in the presence of splenomegaly. Eight to ten doses of carbon tetrachloride were usually necessary to produce ascites and

experiments were performed 14-21 days after the onset of ascites had been recorded.

This cirrhotic model has been characterised in this department (7). Rats treated with carbon tetrachloride as above for 8 to 10 weeks who had evidence of ascites and splenomegaly were studied. In one set of experiments 6 such rats were compared to 6 rats treated only with phenobarbitone. The portal venous pressure was measured by cannulating the ileo-colic tributary of the portal vein and %portasystemic shunting was measured by injecting radioactive microspheres into the portal vein cannula. The cirrhotic rats were found to have a portal venous pressure of 14.8+1.1 mmHg and portasystemic shunting of 25.4+4.7% (7). These animals had abnormal liver function and the results of liver function tests in the previous characterisation studies are shown in Table 9. In a further series of experiments radioactive microspheres were used to measure cardiac output and portal venous inflow in 6 cirrhotic and 6 phenobarbitone treated rats. This method is also used in the current work and is described fully later. The cirrhotic rats had a hyperdynamic circulation with a cardiac output of 172.5±45.4 ml/min (controls 116.7±20.9ml/min) and a portal venous inflow of 13.2±1.3 ml/min (controls 9.2±1.6 ml/min) (7).

Liver biopsy and blood for liver function tests were taken from each carbon tetrachloride treated rat used in the current experiments. Figure 9 shows the histology of the

liver in one rat treated with carbon tetrachloride. The liver function tests were abnormal and are detailed later in this thesis (Table 20).

Table 9- Liver function tests in the previously characterised rat model of cirrhosis (7). Ten rats treated with carbon tetrachloride and phenobarbitone for eight to ten weeks until they had evidence of ascites and splenomegaly (cirrhotics) were compared with ten rats given phenobarbitone only(controls). ALT=alanine transaminase. AST=aspartate transaminase. Values are mean±standard error and the results in the two groups were compared using Mann Whitney U tests. $p<0.05$ is taken to be significant.

LIVER FUNCTION TEST	CIRRHOTICS	CONTROLS	p
Bilirubin(μmol/l)	20.2±2.3	10.3±1.2	0.01
Protein(g/l)	42.3±2.5	65.1±1.2	0.001
Albumin(g/l)	16.6±1.4	31.8±1.4	0.001
ALT(units/l)	114.4±17.5	37.1±1.8	0.001
AST(units/l)	245±39.7	113.1±4.5	0.001
Alkaline Phosphatase (units/l)	438±58.9	93.8±9.8	0.001

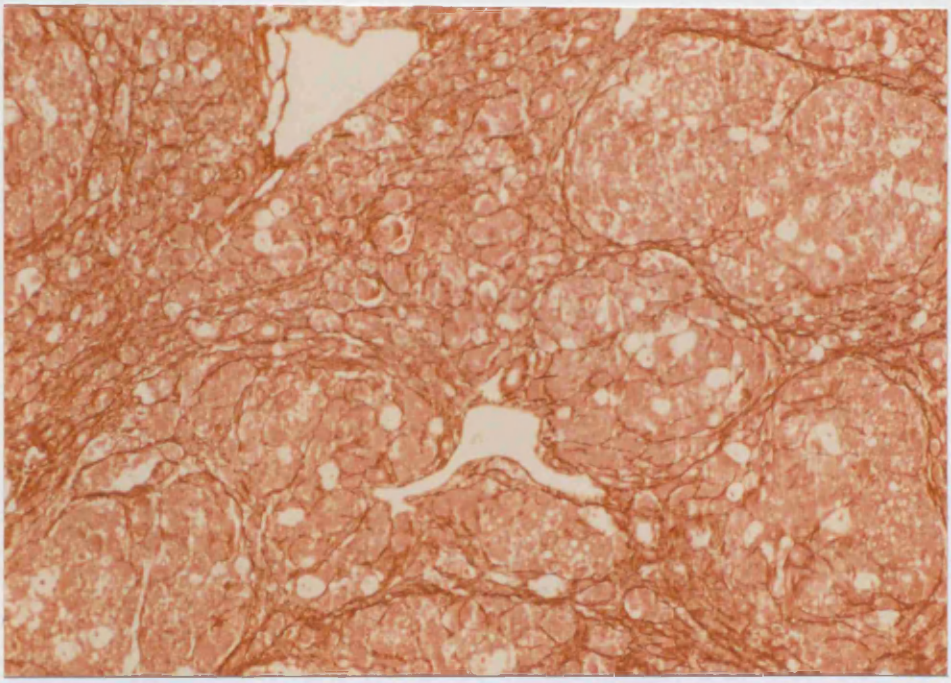

Figure 9 - Reticulin stain of a section of the middle lobe of the liver in a rat treated with carbon tetrachloride for eight weeks, with ascites and splenomegaly.

CHAPTER 5

METHODS USED IN ANIMAL HAEMODYNAMIC STUDIES

INTRODUCTION

As indicated in Chapter 3, SMS 201-995 appears to be an effective means of reducing portal pressure in human cirrhosis. However little is known of its mode of action. Some animal work has been undertaken in an attempt to clarify this. Shield's group have reported that SMS 201-995 does decrease portal pressure in cirrhotic rats (131) and in normal pigs (132). In these studies, portal vein flow was measured using an electromagnetic flow meter around the portal vein and portal pressure was measured via a cannula in the ileo-colic vein. Portal venous resistance was calculated by dividing the portal pressure by portal venous flow and splanchnic vascular resistance was calculated by dividing the mean arterial pressure by the portal vein flow. By this means it was calculated that SMS 201-995 increased splanchnic vascular resistance but had no effect on portal vein resistance and it was felt that its action was probably to constrict pre-splanchnic arterioles. However this method makes no allowance for the effects of portasystemic shunting and if this is significant portal venous inflow will be greater than portal vein flow and thus splanchnic vascular resistance will be overestimated.

With the development of radioactive microspheres for the measurement of blood flow in small animals (235,236,24), it is possible to measure blood flow through both the liver itself and through the portasystemic shunts. A better picture of systemic and portal haemodynamics can be built

up. Cardiac output is determined by the injection of microspheres into the left ventricle while a reference sample is removed over a known time from a large artery. The radioactivity in the reference sample is then used to calculate cardiac output by comparison with the total amount injected. This method also enables the calculation of organ blood flows by measurement of the organ activity in comparison with the reference sample. It is assumed that all the microspheres are well mixed before becoming trapped on the first pass through the peripheral vessels, that they are distributed in proportion to cardiac output and that they do not disturb haemodynamics. The method enables measurement of organ flows without the problems of distortion inherent in the placement of an electromagnetic flow meter round a small vessel. It can be further applied to measure portasystemic shunting by the injection of a second microsphere into the portal vein and measurement of the activity in the liver and the lungs. These methods combined allow the study of drug effects on hepatic artery flow, portal vein flow, shunt blood flow and total hepatic blood flow.

This chapter discusses the general methods used in the conduct of the haemodynamic studies performed in animals and Chapter 6 reports the details of these studies and discusses their results.

CONDUCT OF HAEMODYNAMIC STUDIES.

Fasting

All rats were fasted for at least twelve hours prior to the experiments. This was intended to eliminate variation in portal venous inflow due to increased splanchnic flow following food intake and also meant that washing out the organs before weighing was easier.

Anaesthesia

During some initial pilot work intra-peritoneal pentobarbital was used as an anaesthetic agent with the animal breathing spontaneously, but this gave an unreliable depth of anaesthesia and large variations in the animals' blood gases were seen. Halothane and a mixture of 2:1 nitrous oxide and oxygen was used for all the experiments to be described in this thesis. In dogs, it has been established (237) that halothane can reduce cardiac output, and therefore liver blood flow, in a dose dependent manner. A concentration of 0.5% inspired halothane was shown to cause no significant depression in cardiac output or total peripheral resistance though a significant reduction in both parameters occurred at a concentration of 1.5%. However concentrations up to 2% did not alter portal venous pressure significantly. A standard concentration of 0.5% halothane was used for maintenance of anaesthesia in all of our experiments to avoid possible variations due to the anaesthetic.

Blood gases

Cooperman (238) has pointed out that changes in blood pCO causes changes in the splanchic circulation with hypercarbia causing vasoconstriction, except during halothane anaesthesia, when vasodilatation occurs. Therefore attempts were made to normalise blood gases as far as possible in order to avoid this source of error. This was achieved by performing a tracheostomy and ventilating the rat using a Harvard ventilator (model 683) at a rate of 25-35/min with a tidal volume of 2-3.5ml. A Corning blood gas analyser (model 165) was used to monitor blood gases.

Body temperature

Rectal temperature was read at intervals of five minutes using a mercury thermometer throughout the experiments and a heating lamp was used to maintain the temperature between 36.5 and 37.5°C. A reduction in body temperature will cause mechanisms for heat preservation to come into play and thus change systemic haemodynamics.

Systemic blood pressure

Since hypotension will cause changes in blood distribution due to autoregulatory mechanisms and this will affect splanchnic blood flow, animals with a mean arterial blood pressure of less than 75mmHg during the experiment were excluded from the analysis of the results.

MEASUREMENT OF MEAN ARTERIAL PRESSURE AND PORTAL VENOUS PRESSURE.

Mean arterial pressure was constantly monitored during all experiments. This was performed via a polyethylene femoral artery cannula (outer diameter 0.96mm) connected to a Statham strain gauge transducer and a Gould transducer amplifier (model 13-4615-50) and recorder (8000S series). This was calibrated daily using a mercury manometer. Characteristic fluctuation of the recording from systolic to diastolic pressure was necessary to ensure a satisfactory recording.

Portal venous pressure was monitored using a polyethylene cannula (outer diameter 0.96mm) inserted into the ileo-colic vein and fed upwards into the superior mesenteric vein below the junction with the splenic vein (see Figure 6). This was connected via another Statham strain gauge transducer to the other channel of the Gould recorder. Calibration for the portal venous pressure range (0-25 cm saline) was performed before each experiment using a specially made manometer giving a pressure of 25cm of water. During each experiment it was ensured that respiratory fluctuation of the portal pressure was occurring and that it was possible to withdraw blood from the portal vein via the cannula.

Systolic and diastolic pressures were measured by reading ten values at twelve second intervals from the recording over the two minutes at the end of the period for which measurement was to be made. Pulse pressure was obtained for

each reading by subtracting diastolic from systolic pressure and mean arterial pressure was calculated by adding one third of the pulse pressure value to the diastolic value. Thereafter the mean of the ten readings was calculated and taken as the mean systolic, diastolic, pulse or mean arterial pressure at the end of the period of measurement. Ten values for the maximum and minimum portal pressures were read in a similar manner and mean portal pressure for each reading taken as the average of the maximum and minimum readings. A mean portal pressure at the end of each period of measurement was calculated as above.

THE USE OF GAMMA-LABELLED MICROSPHERES FOR HAEMODYNAMIC MEASUREMENTS.

Microspheres are spherical beads which are obtainable in different sizes and can be labelled with a number of radio-active isotopes. These isotopes emit radiation, including gamma rays, during the radio-active decay process. During these experiments plastic microspheres (New England Nuclear) with a diameter of 15±1 microns (manufacturer's size) and labelled with Cobalt-57, Gadolinium-153 or Tin-113 were used to measure blood flow.

Rat capillaries are known to have a mean diameter of approximately 8 microns (239) and so microspheres of a slightly greater diameter will lodge in the first capillary circulation available after injection into the bloodstream. If streamlining of the flow of microspheres is present their distribution to target organs following injection will reflect the capillary blood flow to that organ.

Microspheres injected into the left ventricle will be distributed by the arterial circulation and give a measure of arterial blood flow to any organ. If blood is withdrawn from the arterial circulation at a known rate, comparison of the radio-activity of the blood withdrawn to that of a particular organ will give an absolute value for its blood flow. If a known number of microspheres is injected the cardiac output can also be calculated.

In normal rats with no portasystemic shunting, the hepatic sinusoids will trap all the microspheres injected into the

portal vein. However if portasystemic shunting is present, some microspheres will travel to the lungs via the shunts and be trapped in the lung capillaries. The ratio of microspheres in the lungs to that in the liver and lungs gives a measure of portasystemic shunting.

Counting

Counting of radioactivity in blood and tissue samples was performed using a gamma scintillation counter (Autogamma 500, Packard Instruments Ltd). Blood samples and the saline used to wash out the syringes were placed directly into plastic counting vials. The hubs of the syringes used for the injection of microspheres and blood sampling were also placed in vials for counting. Organs were washed free of food debris, weighed (Sartorius scales, model 2254) and chopped finely before the counting vials were filled half full of tissue. Counting took place over five minutes per sample using an open energy window (15-2000 keV) if only one radioactive isotope had been injected. An empty, clean vial was counted with each batch of experimental samples, to obtain the current background radioactivity count. This value was subtracted from the value obtained for each experimental vial.

Problems

Several problems in the use of radio-active microspheres for haemodynamic measurements must be considered.

i) Aggregation

Microspheres adhere and clump together easily and this is a major potential source of error due to lack of uniform distribution. The presence of clumping can be established by examining a drop of microsphere solution under a light microscope. Clumping occurs more often when microspheres are suspended in saline solutions and it was therefore necessary to suspend the microspheres in high molecular weight solution (10% w/v dextran-40 in 5% dextrose, Rheomacrodex, Pharmacia) to which 0.01% of the surfactant 'Tween-80' (BDH) had been added to minimise clumping. Despite this, microsphere suspensions aggregated when left standing for prolonged periods and therefore the microsphere solution was always vortex-mixed (Spinmix, Gallenkamp) for three minutes before injection.

ii) Leaching

Leaching is the separation of the radio-isotope from the microspheres and this process increases with the age of the microspheres. Although the microspheres will be trapped in the capillaries of the target organs the radio-isotope will continue to circulate and inaccurate results will be obtained. A monthly check was performed on each batch of microspheres, by centrifugation of the suspension and measuring the activity in the supernatant, to ensure that leaching was not present. The presence of less than 1% of total activity in the supernatant was regarded as acceptable. .When microspheres were only being injected into the portal circulation a further check was possible with each experiment by removing the kidneys and counting them in the gamma scintillation counter. Since all the microspheres injected into the portal system should have lodged in the capillary circulation of the liver or the lungs the kidney counts in these experiments should have been the same as the background count. If the kidney counts were more than 50% above the background count leaching was suspected and the results excluded from analysis.

iii) Streaming

For accurate haemodynamic measurement the microspheres must be evenly distributed throughout the column of blood in a given vessel. This is particularly important during the measurement of cardiac output and organ blood flow using microspheres. By checking that the blood flow to each kidney was equal to within 10% of the total renal blood flow, and excluding the experiments where this was not the case, adequate mixing of microspheres was ensured.

iv) Spillover

In experiments where two radioactive microspheres were used the organs and blood removed for measurement of radioactivity required to be counted with regard to each microsphere. Figure 10 shows the energy peaks of commonly used radio-isotopes and the energy windows of the gamma scintillation counter were set appropriately for the microsphere used. However as spillover of radioactivity from one peak to another occurs correction for this was needed. This was achieved by counting pure samples of the two microspheres used and calculating expected spillover counts for each of the organ samples counted. Spillover counts were then subtracted from the total counts for each organ for each energy window and corrected counts for each microsphere obtained.

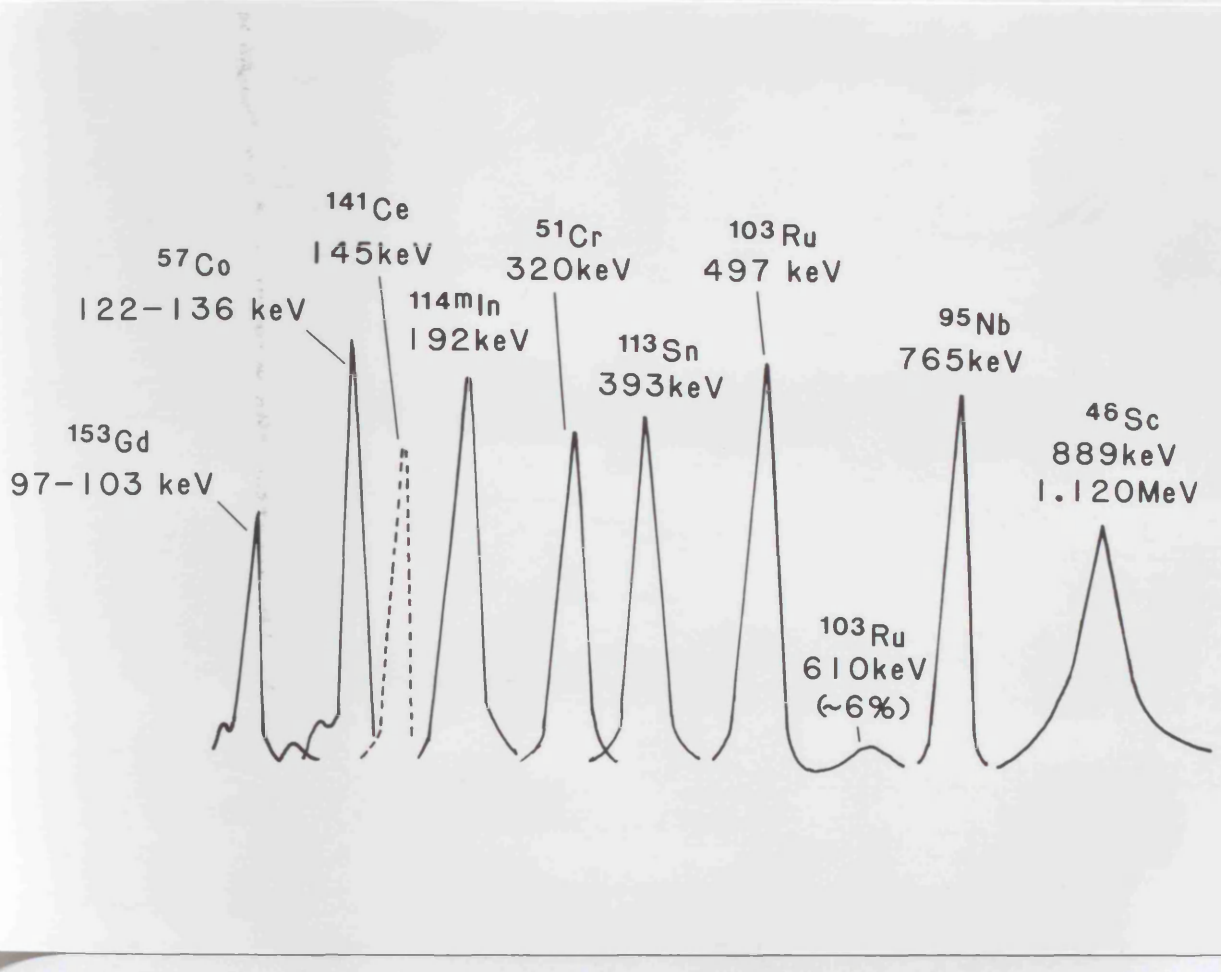

Figure 10 - The energy peaks of gamma radiation from the commonly used radioactive isotopes.

DRUG LEVELS

Five ml blood samples were taken from all animals given a fixed drug dose. These were taken into lithium heparin bottles immediately before sacrifice and the samples spun down immediately. The plasma was then stored at -20°C till analysis. SMS 201-995 levels were measured for each sample using a radioimmunoassay kit supplied by Sandoz Horsforth.

This assay uses polyclonal antiserum raised in the rabbit to SMS 201-995 coupled to bovine serum albumin (219). At the 95% confidence level detection is limited to about 5pg/ml with a 0.1ml aliquot of human blood plasma. Within assay and between assay variability at the 25pg/ml dose level has been found to be 5% and 10% respectively (219). Specificity has been tested with some available synthetic peptide derivatives which could possibly originate from biotransformation (219). One single metabolite was available from work ongoing by Sandoz in metabolism. There was little interaction with the antiserum using the peptide fragments with the partial sequence of the unchanged compound. However, a synthetic product ([Tyr] -analogue) was of equal affinity to SMS 201-995.

CHAPTER 6

THE EFFECTS OF SMS 201-995 IN NORMAL RATS AND TWO RAT MODELS OF PORTAL HYPERTENSION

THE EFFECT OF SMS 201-995 ON CARDIAC OUTPUT AND ORGAN BLOOD FLOWS IN NORMAL RATS

Introduction

The aim of this experiment was to establish whether SMS 201-995 affected systemic haemodynamics in normal rats. Normal rats were given an intravenous infusion of saline or SMS 201-995 at three doses, the lowest approximating to three times the dose used in man. Arterial blood pressure was measured before the infusion and after twenty minutes of infusion, and radioactive microspheres were injected into the left ventricle to measure cardiac output and organ blood flows at the end of the infusion period.

Materials and methods

58 male Sprague-Dawley rats, ranging in weight from 280-410g, were used in these experiments. The results from 35 rats were excluded from analysis because of technical problems discussed below and the results from three groups of six and one group of five rats, were analysed. All animals were fasted for at least 12 hours prior to the study. Anaesthesia was induced in a perspex box using 2% halothane and a mixture of 2:1 nitrous oxide and oxygen. A tracheostomy was performed and the rat was then ventilated using 2:1 nitrous oxide and oxygen and 0.5% halothane. A heating lamp was used to maintain rectal temperature between 36.5 and 37.5°C. Both femoral arteries and one femoral vein were cannulated using polyethylene cannulae (OD 0.96mm). The right carotid artery was cannulated using a further length of polyethylene cannula and the cannula advanced into the left ventricle under continuous arterial pressure monitoring. An abrupt change in the pressure tracing from an arterial to a left ventricular form was seen when the cannula passed through the aortic valve (Figure 11). The distance from the carotid artery at the level of the first tracheal ring to the left ventricle has been stated by previous workers (235) to be 4.2cm and it was found helpful to mark the cannula 4.2cm from its tip to show when the aortic valve was being approached. The rat was heparinised with 130 units/100g body weight sodium heparin. One femoral artery cannula was used for monitoring of arterial pressure,

the other was used for withdrawal of the reference sample and the femoral vein cannula for drug infusion (Figure 12). 0.3ml of arterial blood was then withdrawn from one of the femoral artery cannulas for blood gas estimation. Thereafter the experiment proceeded only if mean arterial pressure was greater than 75mmHg, pH was greater than 7.3, pO_2 was greater than 100mmHg and pCO_2 was between 33 and 42mmHg. When these conditions were achieved a 20 minute infusion of normal saline, or SMS 201-995 1µg/kg/hr, 2µg/kg/hr, or 4µg/kg/hr was commenced via the femoral vein cannula, using a Braun pump (type 871014). Each dose of SMS 201-995 or saline was given to one group of rats, 4µg/kg/hr being given to the group of five. The total volume infused was 1ml.

At the end of the 20 minute period a bolus of 0.2ml of radio-active microspheres (Gd-153 or Co-57) in 10% dextran was injected into the left ventricle over 20 seconds followed by a 0.2ml saline flush. The radio-activity in a 0.5ml aliquot of these microspheres had already been measured in the gamma scintillation counter prior to the experiment. 0.2ml of microsphere solution from this aliquot was drawn up into a syringe immediately before use and this sample vortexed for three minutes before injection. Ten seconds prior to injection the withdrawal of a reference sample of blood from the second femoral artery cannula was commenced (Harvard pump model 1901A) and this continued for 70 seconds at a rate of approximately 1ml/min. Two minutes after the injection of the microspheres 5ml of blood was

removed from the first femoral artery cannula for SMS 201-995 levels and then the animal was killed using an intravenous bolus of 0.5 ml saturated potassium chloride solution. The position of the left ventricular cannula was checked. The brain, lungs, liver, spleen, stomach, small and large bowel, mesentery and kidneys were removed. The bowel was emptied of any residual food particles by gentle washing in water and the organs weighed on a balance (Sartorius model 2254). The tissue samples were cut into small pieces and placed in vials for counting in the gamma scintillation counter.

The residue of the 0.5ml aliquot of microspheres, the washout of the syringe(3 washes with water) used to inject the microspheres, the syringe itself and the needle used for injection were also counted. The reference sample syringe was weighed with the sample inside and the weight of the sample obtained by subtracting its weight when empty.

The reference sample, three washes of its syringe with water and its syringe, needle and cannula were placed in vials for counting. In this experiment counting took place over five minutes per vial and used an open energy window (lower limit 15keV: upper limit 2000keV). The total amount of activity injected was calculated by subtracting the activity left in the syringe and needle used for injection, the activity of the washout from that syringe and the activity of the residue of the initial 0.5ml of microspheres. The reference sample activity was calculated

by adding the activity of the blood in the sample, the activity of the syringe washouts and the activity in the reference syringe, needle and cannula. The reference sample flow was calculated by dividing the weight of the sample by blood density (1.1g/ml) and then dividing by the time of withdrawal in minutes.

Mean arterial blood pressure before the infusion began and at twenty minutes thereafter, was calculated. Cardiac output and organ blood flows were then calculated.

Cardiac Output = (ref sample flow/ref sample activity)
× total amount of activity injected.

Organ blood flow =
(ref sample flow/ref sample activity) × organ activity

Portal venous inflow was calculated from the sum of the blood flows to the splanchnic organs.

Both kidneys were measured to check for adequate mixing of microspheres. Where the difference between the right and left kidney flows was greater than 10% of the total kidney flow the experiment was discarded. Since it is essential that the intraventricular injection of microspheres does not disturb haemodynamics any experiments where there was a fall in arterial blood pressure of greater than 10 mmHg during or after the injection of microspheres were excluded.

Mean arterial blood pressure in the four groups of rats at

time zero were compared using analysis of variance to ensure that the groups of rats were comparable in this respect. Mean arterial blood pressure after 20 minutes was compared between the groups by performing Wilcoxon signed rank tests between zero and the change in blood pressure after 20 minutes. The results of the cardiac index and portal venous inflow measurements in the four groups were compared using the Kruskal Wallis test. Results were taken to be significant if $p<0.05$.

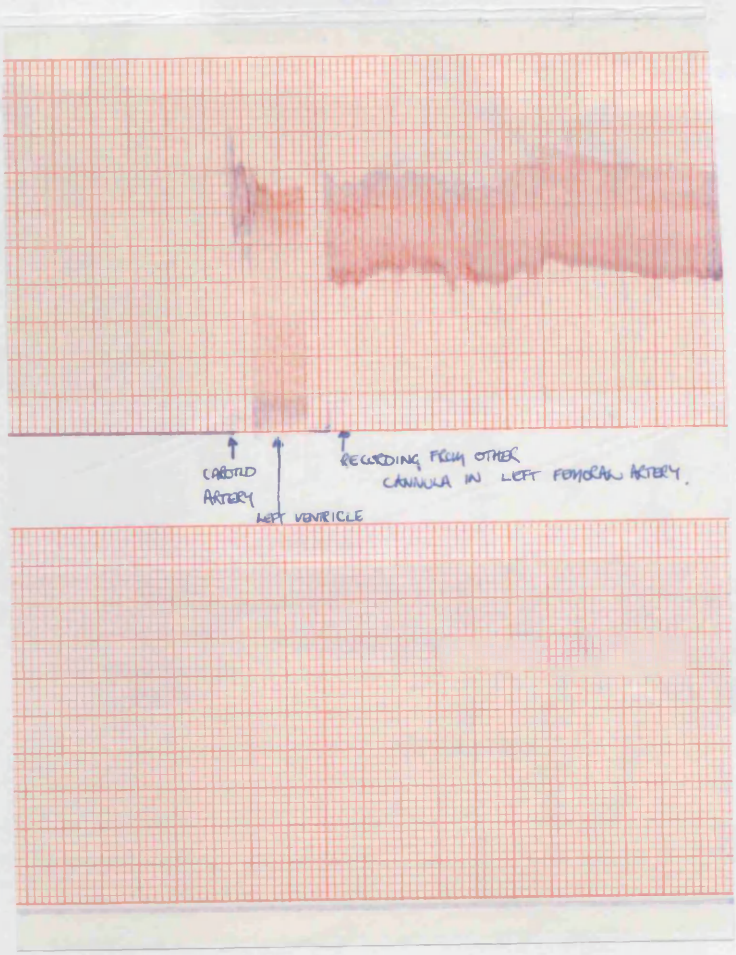

Figure 11 - The tracing from the Gould recorder showing arterial pressure during insertion of the cannulas. Paper speed 5mm/min. Vertical scale 25mmHg/mm. This tracing was taken during cannulation of the left ventricle for cardiac output estimation and shows the change in the pressure waveform as the cannula moved from the carotid artery through the aortic valve into the left ventricle.

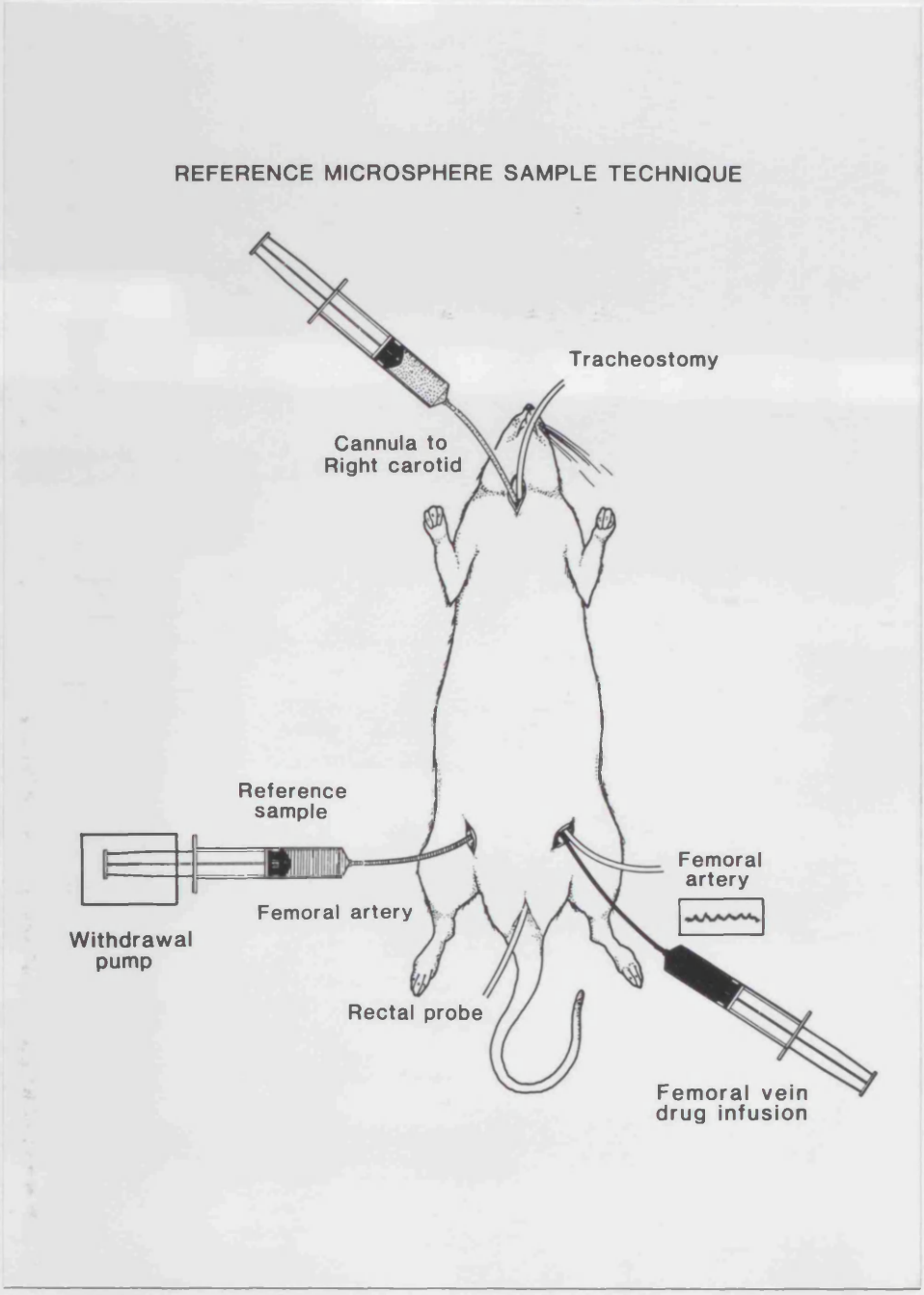

Figure 12 - The experimental lay-out for the measurement of cardiac output and organ blood flow in the rat.

Results

From a total of 58 rats used in these experiments, the results from 35 rats were excluded for the following reasons. 13 rats had evidence of damage to the ventricular septum with very high lung radioactivity. In two rats arterial blood pressure dropped by more than 10mmHg during the microsphere injection. In 10 rats the kidney counts were unequal by more than 10% of renal blood flow. In four rats an adequate reference sample was not obtained because of kinking or clotting of the cannula or malfunction of the pump. In six rats the left ventricular cannula was not in the ventricle at the end of the experiment.

Tables 10, 11 and 12 are a summary of the results of this experiment in the 23 rats whose results were analysed. Appendix 3 shows the results for individual rats for mean arterial blood pressure, cardiac index and portal venous inflow. When mean arterial blood pressure in the four groups of rats at time zero is considered, the F-ratio from the analysis of variance is non-significant at the 0.05 significance level. After the infusion of saline or SMS 201-995 Wilcoxon signed rank tests on the differences in mean arterial pressure showed no significant change (Table 13). Cardiac index values are widely scattered (Figure 13). The test statistic from the Kruskal Wallis test comparing the cardiac index in the four groups was 3.6 and when referred to the Chi-squared distribution with 3 degrees of freedom, proves to be non-significant at the nominal 0.05

significance level ($p<0.4$). When portal venous inflow as a percentage of cardiac output is examined there perhaps is a trend towards a reduction in portal venous inflow with increasing doses of SMS 201-995 (Figure 14). However the test statistic from the Kruskal Wallis test was 0.35 and when referred to the Chi-squared distribution with 3 degrees of freedom, proves to be non-significant at the nominal 0.05 significance level ($p<0.97$). With regard to the individual organ blood flows, no difference between the groups can be seen.

Plasma levels of SMS 201-995 were less than 100pg/ml in all the rats in the control group. In the groups given SMS 201-995 the mean plasma level was 1014pg/ml(sem 341) in the group given 1µg/kg/hr, 1920pg/ml(sem 329) in the group given 2µg/kg/ml and in the group given 4µg/kg/ml two of the five rats had plasma levels of >2500mg/ml, while the other three values were 1950, 2150 and 2150pg/ml.

Table 10 - Weight and blood gases in the four groups of rats who had arterial blood pressure, cardiac index and organ blood flows measured after a 20 minute infusion of saline or 1, 2 or 4μg/kg/hr SMS 201-995. Weight is shown in grams and pCO_2 is shown in mmHg.

	CONTROL GROUP	1μg/kg/hr	2μg/kg/hr	4μg/kg/hr
NUMBER	6	6	6	5
WEIGHT (mean+sem)	348.2±18.2	319.8±13.1	334.5±13.5	325.4±13.8
pH median (range)	7.4 (7.33-7.58)	7.35 (7.24-7.52)	7.33 (7.27-7.46)	7.35 (7.26-7.4)
pCO (mean+sem)	34.6±2.1	39.1±0.5	35.2±2.3	36.4±1.5
BASE EXCESS (mean+sem)	-1.1±2.9	-1.6±2.4	-5.6±2.6	-3.7±1.9

Table 11 - The effect of SMS 201-995 on mean arterial pressure, cardiac output and portal venous inflow in normal rats. Dose of SMS 201-995 is shown in ug/kg/hr. Arterial pressure is shown in mmHg at 0 and 20 minutes. Cardiac index(CI) is shown in ml/kg/min. Portal venous inflow(PVI) is shown in ml/min and as %cardiac output(CO). All values are mean ± standard error.

	CONTROL GROUP	1ug/kg/hr	2ug/kg/hr	4ug/kg/hr
MEAN ARTERIAL PRESSURE 0	104.2±7.4	94.2±6.2	93.3±4.0	93±11.8
20	102.5±7.6	90.8±7.6	85±7.2	97±10.4
CARDIAC INDEX	205.1±16.2	259.6±35.6	324.8±73.7	213.7±31.1
PORTAL VENOUS INFLOW	10.4±1.1	11.3±1.0	11.8±1.1	8.8±1.3
PVI AS % CO	14.6±0.3	14.2±1.3	12.7±1.7	13.0±1.7

Table 12 - The effect of SMS 201-995 on organ blood flow in normal rats. Dose of SMS 201-995 is shown in μg/kg/hr. Organ blood flow is shown in ml/kg organ weight/min. All values are mean ± standard error.

	CONTROL GROUP	1μg/kg/hr	2μg/kg/hr	4μg/kg/hr
BRAIN	0.9±0.08	1.4±0.3	1.6±0.4	0.8±0.1
LUNG	1.0±0.3	2.3±0.4	1.5±0.3	2.4±1.0
HEPATIC ARTERIAL	0.3±0.05	0.3±0.05	0.3±0.03	0.3±0.07
SPLEEN	1.1±0.1	0.9±0.1	0.9±0.06	1.2±0.3
STOMACH	0.3±0.05	0.5±0.06	0.4±0.08	0.4±0.03
SMALL BOWEL	0.7±0.07	0.9±0.05	0.8±0.05	0.7±0.1
CAECUM	0.8±0.1	0.8±0.07	0.9±0.1	0.7±0.1
COLON	0.5±0.04	0.5±0.03	0.5+0.06	0.4±0.07
MESENTERY	0.4±0.04	0.4±0.04	0.5±0.1	0.3±0.06
RENAL	5.2±0.4	4.8±0.2	6.4±0.8	4.5±0.2

Table 13 - Results of Wilcoxon signed rank tests on differences in mean arterial blood pressure after a 20 minute intravenous infusion of saline 1, 2 or 4 µg/kg/hr SMS 201-995.

	WS	p
CONTROL GROUP	6.0	0.79
1µg/kg/hr	4.5	1.0
2µg/kg/hr	5.0	0.29
4µg/kg/hr	3.0	0.37

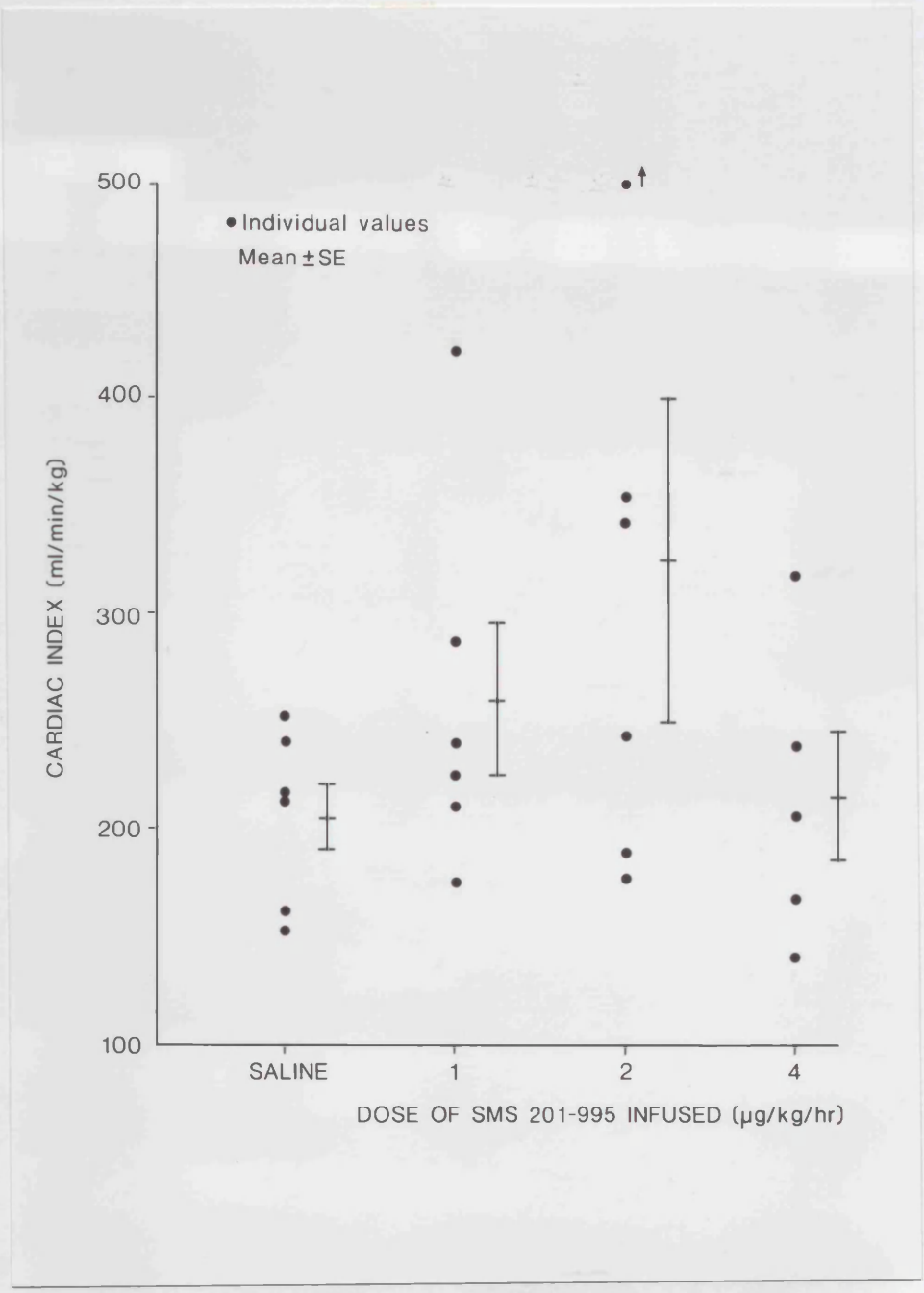

Figure 13 - Cardiac index in four groups of normal rats following a 20 minute intravenous infusion of saline or 1µg/kg/hr, 2µg/kg/hr or 4µg/kg/hr SMS 201-995. n=6 for each group except the 4µg/kg/hr group where n=5. Cardiac index shown in ml/min/kg.

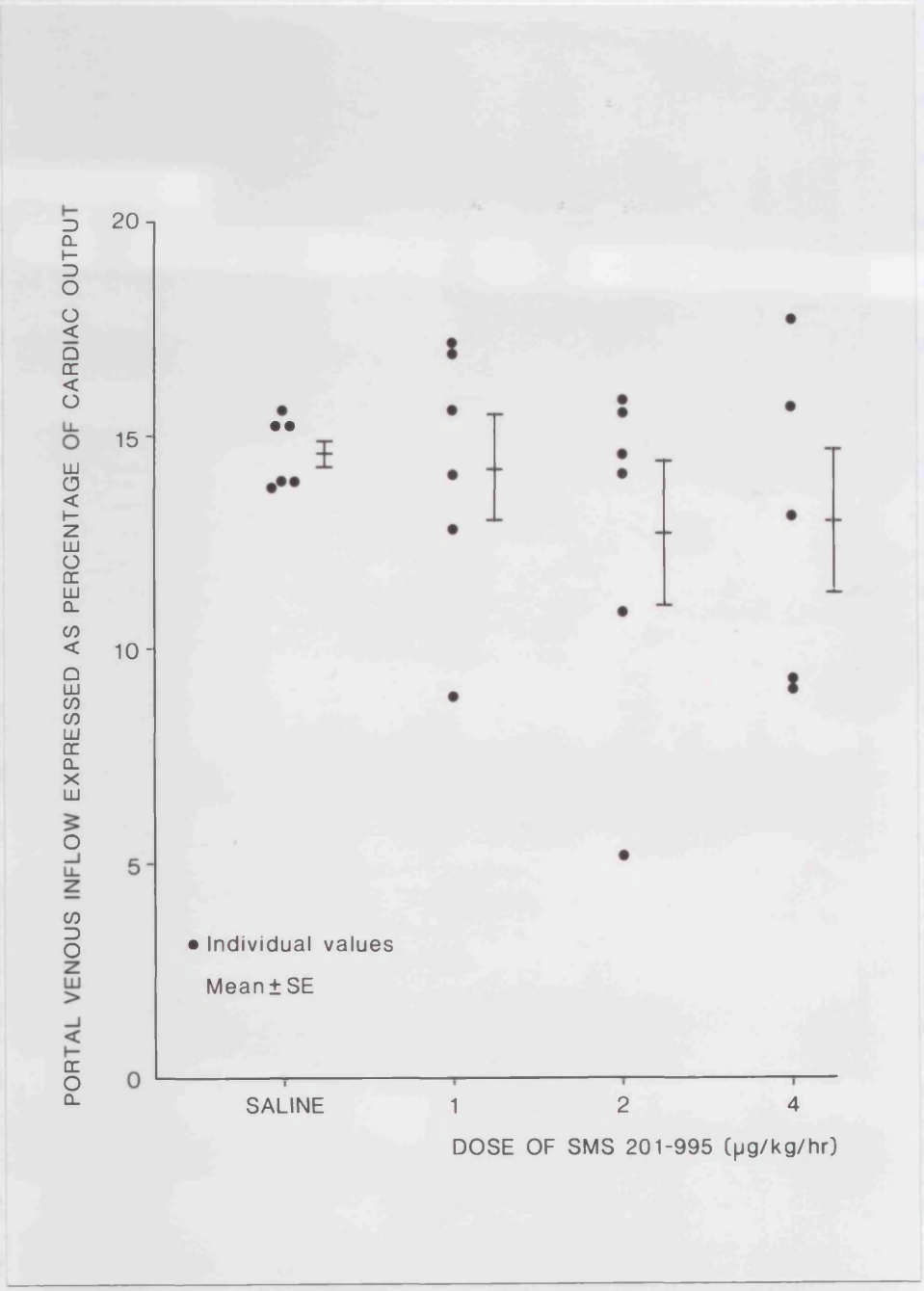

Figure 14 - Portal venous inflow calculated as the percentage of cardiac output in four groups of normal rats following a 20 minute intravenous infusion of saline or 1µg/kg/hr, 2µg/kg/hr or 4µg/kg/hr SMS 201-995. n=6 in each group except the 4µg/kg/hr group where n=5.

Discussion

In this experiment SMS 201-995 did not affect systemic arterial blood pressure or cardiac output. This is in keeping with previous reported results from Jenkins and colleagues in cirrhotic rats (131) and from Mountokalakis and Levy in normal dogs (136). In another report Jenkins and colleagues showed a reduction in cardiac output in normal pigs after a 20 minute intravenous infusion of 250µg/hr SMS 201-995 (132). Assuming the weight of the pigs to be around 50kg this is approximately ten times the dose normally used in man and this large dose may explain the effect seen. Three doses have been used in this study, the smallest of which is approximately three times the dose used in man, but no significant effect on cardiac output in normal rats has been demonstrated.

Although there was a trend towards a reduction in portal venous inflow after increasing doses of SMS 201-995 this was not statistically significant. Jenkins' previous work in cirrhotic rats showed a significant reduction in portal venous flow and liver blood flow (131), but he took no account of shunt blood flow and cirrhotic animals may well react differently from normals because of abnormal liver function and portasystemic shunting.

SMS 201-995 levels in the 2 and 4µg/kg/hr groups were higher than the SMS 201-995 levels found in stable cirrhotic patients where the mean plasma level of SMS 201-995 at the end of 60 minutes infusion was 1515±280pg/ml when

transhepatic venous gradient was significantly reduced from baseline values.

THE EFFECT OF SMS 201-995 ON PORTAL PRESSURE IN NORMAL RATS.

Introduction

This experiment was performed to show whether SMS 201-995 has an effect on portal pressure in normal rats. Portal and systemic arterial pressure was monitored during the intravenous infusion of increasing doses of SMS 201-995.

Materials and methods

Twenty-three male Sprague-Dawley rats, each weighing between 280g and 420g, were used in these experiments.

On the day of the experiment the rats were fasted for at least twelve hours before anaesthesia was induced in a perspex box with 2% halothane and a mixture of 2:1 nitrous oxide and oxygen. A tracheostomy was performed and the rat was then ventilated using 2:1 nitrous oxide and oxygen and 0.5% halothane. A heating lamp was used to maintain rectal temperature between 36.5 and 37.5°C.

Laparotomy was performed via a lower midline incision and the ileocolic tributary of the portal vein cannulated to record portal pressure. The abdomen was then closed in two layers with chromic catgut. A minimal amount of heparinised saline (500units in 500ml normal saline) was injected into the cannulae to prevent clotting. One femoral artery was cannulated for arterial pressure recording. One femoral vein was cannulated for the drug infusion. Arterial blood gas estimation was performed before the start of the infusion. Thereafter an infusion of saline at a rate of 0.05ml/min was commenced via the femoral vein cannula. Continuous monitoring of portal and arterial pressure took place throughout the study. Twenty minutes of saline infusion was followed in fourteen normal rats by infusion of 1μg/kg/hr, 2μg/kg/hr and 4μg/kg/hr SMS 201-995 using a Braun pump for twenty minute periods at each dose, maintaining the infusion volume at a constant rate (0.05ml/min). The other group of

nine rats were given an eighty minute infusion of normal saline (0.05ml/min). At the end of 80 minutes the rats were killed by a 1ml intravenous bolus of saturated potassium chloride.

Arterial and portal pressures in the two groups were compared at the end of each infusion period using repeated analysis of variance (BDMP Medical statistics package). Results were taken to be significant if $p<0.05$.

Results

Three rats in the control group and eight rats in the study group suffered a rapid drop in arterial pressure and died during the experiment. This was found to be due to blood loss into the peritoneal cavity following portal vein cannulation and these animals' results are not included in the analysis. The data from each rat are shown in Appendix 4 and the results are summarised in Table 14. Analysis of variance for repeated measures demonstrated no significant differences in arterial ($p<0.67$) or portal pressure ($p<0.99$) between the control and study groups. There were no significant changes in arterial or portal pressure with increasing doses of SMS 201-995.

Table 14 - The effect of SMS 201-995 on portal and systemic pressure in normal rats. Arterial pressures are shown in mmHg and portal pressures in cm water. Weight is shown in grams and the dose of SMS 201-995 given to the study group is shown in µg/kg/hr. All values except pH are mean ± standard error.

	CONTROL GROUP	STUDY GROUP
NUMBER	6	6
WEIGHT	355.5±21.5	305.2±7.4
pH(median)	7.35	7.33
(range)	(7.27-7.46)	(7.28-7.37)
pCO	36.1±1.2	33.3±1.8
BASE EXCESS	-5.7±2.1	-7.5±1.5
MEAN ARTERIAL PRESSURE		
20min/Saline	96.9±7.3	101.1±5.8
40min/1µg	99.3±4.4	95.4±5.5
60min/2µg	96.5±7.9	93.1±8.0
80min/4µg	95.1±1.6	84.6±11.1
MEAN PORTAL PRESSURE		
20min/Saline	7.4±1.1	7.2±1.1
40min/1µg	7.4±0.9	7.9±0.7
60min/2µg	8.4±0.9	8.3±0.4
80min/4µg	7.8±0.8	7.7±0.5

Discussion

This experiment could demonstrate no effect of SMS 201-995 on portal pressure in normal rats. Although there was a slight fall in mean arterial pressure in rats given SMS 201-995, this was not statistically significant and no significant difference from the arterial pressures in the control group was demonstrated.

One previous group has reported similar work, on the effects of SMS 201-995 infusion on portal pressure in sham operated rats (240) who served as controls for partial portal vein ligated and bile duct ligated groups. In Cerini and colleagues experiments the measurements were performed on unanaesthetised animals and increasing doses of SMS 201-995 from 0.25 to 16μg/kg/hr were infused for 10 minutes per dose. In sham operated rats no significant difference in portal pressure was seen.

However in normal pigs a significant reduction in portal pressure after infusion of 250μg/hr of SMS 201-995 for 20 minutes has been reported (132). These differences may be due to the species of animal used . The dose of SMS 201-995 used by Jenkins and colleagues is also considerably higher than the dose we have used.

THE EFFECT OF SMS 201-995 ON PORTAL PRESSURE IN PORTAL HYPERTENSIVE RATS.

Introduction

This experiment was performed to show whether SMS 201-995 has an effect on portal pressure in portal hypertensive rats and to try to establish a dose of the drug to be used in future experiments. Portal and systemic arterial pressure were monitored in rats who had extrahepatic portal hypertension during the intravenous infusion of increasing doses of SMS 201-995.

Materials and methods

Twenty-three male Sprague-Dawley rats, each weighing between 280g and 420g, were used in these experiments. These rats had undergone partial portal vein ligation three days previously.

On the day of the experiment the rats were fasted for at least twelve hours before anaesthesia was induced in a perspex box with 2% halothane and a mixture of 2:1 nitrous oxide and oxygen. A tracheostomy was performed and the rat was then ventilated using 2:1 nitrous oxide and oxygen and 0.5% halothane. A heating lamp was used to maintain rectal temperature between 36.5 and 37.5°C.

Laparotomy was performed via a lower midline incision and the ileocolic tributary of the portal vein cannulated to record portal pressure. The abdomen was then closed in two layers with chromic catgut. A minimal amount of heparinised saline (500units in 500ml normal saline) was injected into the cannulae to prevent clotting. One femoral artery was cannulated for arterial pressure recording. One femoral vein was cannulated for the drug infusion. Arterial blood gas estimation was performed before the start of the infusion. Thereafter an infusion of saline at a rate of 0.05ml/min was commenced via the femoral vein cannula. Continuous monitoring of portal and arterial pressure took place throughout the study. Twenty minutes of saline infusion was followed in nine rats by infusion of 1µg/kg/hr, 2µg/kg/hr and 4µg/kg/hr SMS 201-995 and in seven rats by infusion of

8,16 and 32μg/kg/hr SMS 201-995. Seven rats acted as controls and continued to have saline infused. A Braun pump was used for intravenous infusion for twenty minute periods at each dose, maintaining the infusion volume at a constant rate (0.05ml/min). At the end of 80 minutes the rats were killed by a 1ml intravenous bolus of saturated potassium chloride.

Arterial and portal pressures in the two experimental groups were compared with the values in the control group at the end of each infusion period using repeated analysis of variance(BMDP Medical Statistics Package). Results were taken to be significant if $p<0.05$.

Results

One rat in the control group, three rats in the 1-4μg/kg/hr group and one rat in the 8-32μg/kg/hr group sustained massive blood loss after portal vein cannulation and their results have been excluded from the analysis. The results are summarised in Table 15 and the raw data for each rat are shown in Appendix 5. Figure 15 shows the change in portal pressure with time for each group of rats.

Arterial pressure decreased significantly with time in the control group ($p<0.04$) but this difference was not significantly different from the changes in arterial pressure with time in either the 1-4μg/kg/hr group ($p<0.11$) or the 8-32μg/kg/hr group (0.07).

Portal pressure tended to fall with time, significantly in the control ($p<0.02$) and 1-4μg/kg/hr groups ($p<0.01$). However there was no significant difference in the fall between the control and 1-4μg/kg/hr groups ($p<0.09$) and the fall in the control group was significantly greater than that in the 8-32μg/kg/hr group($p<0.004$).

Table 15 - Weight, blood gases and mean arterial pressure in three groups of portal hypertensive rats given intravenous infusions of either saline, 1-4μg/kg/hr or 8-32μg/kg/hr SMS 201-995. Saline was infused for the first twenty minutes, then either saline or doubling doses of SMS 201-995 for twenty minutes at each dose. Arterial pressures are shown in mmHg. Weight is shown in grams and the dose of SMS 201-995 given to the study groups is shown in μg/kg/min. All values are mean + standard error. n=6 for each group other than the 8-32μg/kg/hr group where n=4.

	CONTROL GROUP	1-4μg/kg/hr	8-32μg/kg/hr
WEIGHT	303±7	289±7.0	269±12
pH(median)	7.29	7.29	7.31
(range)	(7.27-7.3)	(7.2-7.4)	(7.23-7.45)
pCO_2	32±1	33±2	32±3.9
BASE EXCESS	-9±2	-9±2	-7.4±1.8
MEAN ARTERIAL PRESSURE			
Saline	114±5	104±6	117±5
40min/1μg/8μg	106±7	93±4	128±6
60min/2μg/16μg	96±8	94±7	121±4
80min/4μg/32μg	98±10	89±11	121±4

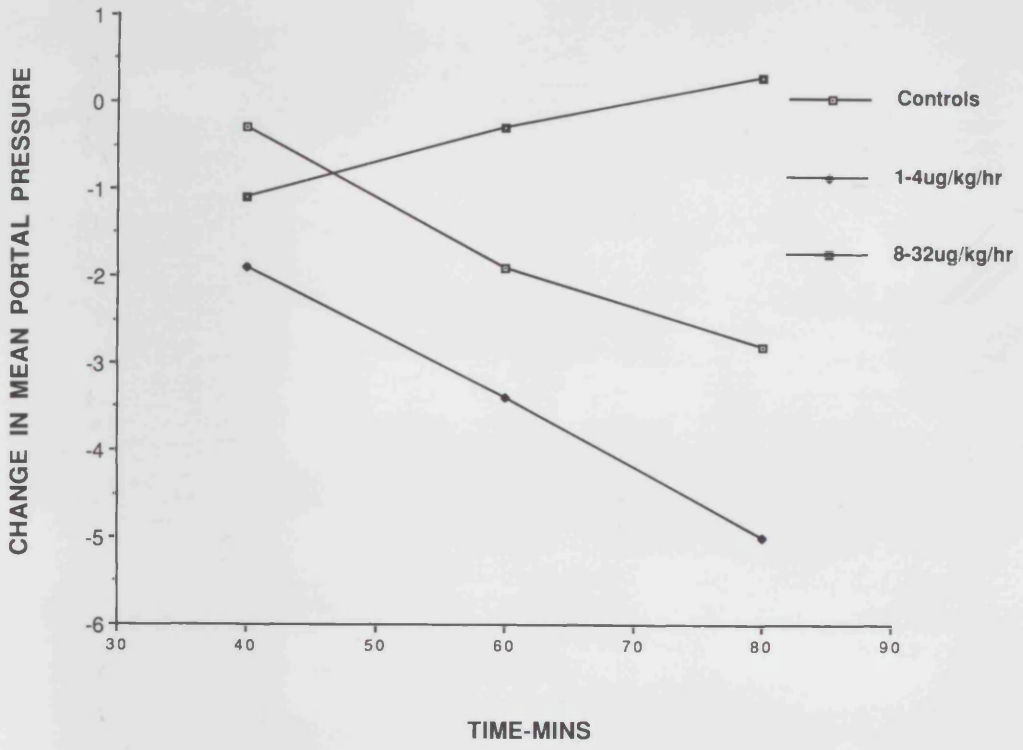

Figure 15 - Change in mean portal pressure with time in three groups of portal hypertensive rats given intravenous infusions of either saline, 1-4µg/kg/hr or 8-32µg/kg/hr SMS 201-995. Saline was infused for the first twenty minutes, then either saline or doubling doses of SMS 201-995 for twenty minutes at each dose. n=6 for each group other than the 8-32µg/kg/hr group where n=4.

Discussion

In portal hypertensive rats the results are less clear. Reductions in portal pressure were seen in both study and control groups, with lesser reductions in mean arterial pressure. Any reduction in portal pressure seemed to greatest in the 1-4μg/kg/hr group, although statistically significant differences between the groups were not seen. For this experiment we used rats three days after portal vein ligation. This meant that a high portal pressure was obtained but it was also noticed that these rats had a higher blood loss due to the ileo-colic vein cannulation than normal rats. Because of this blood loss, the rats were less stable, with a tendency to drop their arterial pressure, and acid-base balance was less satisfactory with a tendency towards metabolic acidosis. These problems occurred in both study and control groups. Previous work in portal hypertensive rats has shown that portal pressure falls to a greater extent than mean arterial pressure after haemorrhage (241) and that in a haemorrhaged-transfused rat model of portal hypertension there is reduced sensitivity to vasopressin (242). This may help to explain our results.

Since a 4μg/kg/hr dose of SMS 201-995 has been used by other groups, did not appear to affect systemic haemodynamics, but seemed possibly to have an effect on portal pressure it was decided to use this dose in the succeeding experiments. Plasma levels of SMS 201-995 had been shown to be satisfactory with a dose of 4μg/kg/hr in

the previous experiment and it was expected that these would be, if anything, higher in portal hypertensive rats.

THE EFFECT OF REPEATED INJECTION OF MICROSPHERES ON PORTASYSTEMIC SHUNTING MEASUREMENTS

Introduction

To establish whether SMS 201-995 affects the degree of portasystemic shunting it was hoped to perform two measurements of %portasystemic shunting in a series of rats given an infusion of SMS 201-995. However it is possible that the injection of microspheres itself will alter the degree of portasystemic shunting by blocking the capillaries. Therefore two measurements of %portasystemic shunting were performed in rapid succession in a group of rats to ensure that successive measurements were comparable.

Materials and methods

Five male Sprague-Dawley rats weighing between 250g and 300g and who had undergone portal vein ligation three days earlier were used in this experiment. The rats were fasted for at least twelve hours prior to the experiment.

Anaesthesia was induced in a perspex box with 2% halothane and a mixture of 2:1 nitrous oxide and oxygen. A tracheostomy was performed and the rat was then ventilated using a mixture of 2:1 nitrous oxide and oxygen and 0.5% halothane. A heating lamp was used to maintain rectal temperature between 36.5 and 37.5°C.

Laparotomy was performed using a lower midline incision and the ileocolic tributary of the portal vein was cannulated. The abdomen was closed in two layers with chromic catgut. One femoral artery was cannulated for arterial pressure recording. A minimal amount of heparinised saline (500 units heparin in 500ml of normal saline) was injected through the cannulae to prevent clotting.

Arterial blood gas estimation was performed after these cannulae were inserted. Experiment proceeded if pH>7.3, pO_2 >100mmHg and pCO_2 was between 33 and 42mmHg.

A bolus of 0.1ml of Co-57 labelled microspheres (1,000 microspheres) was injected into the portal vein cannula followed by a 0.2ml saline flush. Prior to injection the syringe containing the microspheres was vortexed for three minutes. Three minutes later 0.1 ml of Sn-113 labelled microspheres (1,000 microspheres) was injected into the

portal vein followed by a saline flush. Two minutes after the second injection of microspheres the rat was killed by a 1ml intravenous bolus of saturated potassium chloride and the liver and lungs removed.

The lungs and liver were placed in vials for counting in the gamma scintillation counter. Counting took place over ten minutes per sample and using two energy windows 80-150keV for Co-57 and 300-450keV for Sn-113. The error in the measurement of the radioactivity introduced by the spillover of Co-57 energy into the Sn-113 channel and vice versa was corrected by using Co-57 and Sn-113 standards.

% porta-systemic shunting was calculated for each injection by using the formula

% porta-systemic shunting = counts in lung/counts in liver and lung $\times$ 100.

The results for the two injections in each rat were compared using the Mann Whitney U test.

Results

The results are shown in Tables 16 and 17. The maximum difference between the two measurements was 6.6% and the mean difference was 2.6%. A Wilcoxon signed rank test demonstrated no significant difference between the two sets of measurements ($p=0.26$)

Table 16 - The effect of intraportal injection of microspheres on %shunting measurements in portal hypertensive rats. Weight is shown in grams, arterial pressure in mmHg and portal pressure in cm of water. n=5.

	MEAN ± STANDARD ERROR
WEIGHT	267.8±10.4
pH-median(range)	7.3(7.25-7.4)
pCO_2	35.5±0.9
BASE EXCESS	-7.2±0.4
MEAN ARTERIAL PRESSURE	83.6±6.7
MEAN PORTAL PRESSURE	15.8±1.6
% SHUNTING	
Co-57 - 1st INJECTION	81.3±3.6
Sn-113- 2nd INJECTION	83.4±3.3

Table 17 - Comparison of two successive % portasystemic shunting measurements in 5 rats.

RAT NO.	1ST MEASUREMENT	2ND MEASUREMENT	DIFFERENCE
1	78.8	83.3	+4.5
2	75.3	81.9	+6.6
3	73.3	73.0	-0.3
4	92.7	93.2	+0.5
5	86.6	85.7	-0.9
MEAN	81.3	83.4	+2.6%

Discussion

In this experiment there was very close agreement between the first and second measurements of %portasystemic shunting in portal hypertensive rats. Therefore the injection of a small dose of microspheres into the portal system did not itself affect % portasystemic shunting and this microsphere method could be used to evaluate the effect of SMS 201-995 on portasystemic shunting in the rat.

THE EFFECT OF SMS 201-995 ON PORTAL PRESSURE AND PORTASYSTEMIC SHUNTING IN PORTAL HYPERTENSIVE RATS.

Introduction

The aim of this experiment was to establish more clearly whether SMS 201-995 causes a reduction in portal pressure in portal hypertensive rats and whether this is accompanied by a change in the degree of portasystemic shunting in these animals. Portal vein ligated rats at three and twenty eight days post-ligation were used since previous work in this department has shown that %shunting increases and portal hypertension decreases with time after portal vein ligation and it was hoped that animals with a spectrum of values for shunting and portal pressure would be obtained. Following our previous experiments with SMS 201-995, 4µg/kg/hr was chosen as the dose most likely to produce an effect.

Materials and methods

Three groups of six and one group of seven male Sprague-Dawley rats, weighing between 250g and 440g were used in this experiment. Two groups of six had undergone portal vein ligation three days previously. The other 13 rats had undergone partial portal vein ligation twenty-eight days previously. On the day of the experiment the rats were fasted for at least twelve hours before anaesthesia was induced in a perspex box with 2% halothane and a mixture of 2:1 nitrous oxide and oxygen. A tracheostomy was performed and the rat was then ventilated using a mixture of 2:1 nitrous oxide and oxygen and 0.5% halothane. A heating lamp was used to maintain rectal temperature between 36.5 and 37.5°C.

Laparotomy was performed via a lower midline incision and the ileocolic tributary of the portal vein cannulated. The abdomen was closed in two layers with chromic catgut and the portal vein cannula used to record portal pressure and for the injection of microspheres. One femoral artery was cannulated for arterial pressure recording. One femoral vein was cannulated for drug infusion. A minimal amount of heparinised saline (500 units sodium heparin in 500ml normal saline) was injected into the cannulae to prevent clotting.

Blood gas estimations were performed before the infusion began and at 30 minute intervals thereafter. Infusion commenced with normal saline at 0.05 ml/min for 30 minutes in all groups of rats. At the end of this time 0.1 ml Co-57

labelled microspheres (1000 microspheres) in 10% dextran was vortex-mixed for 3 minutes then injected into the portal vein cannula followed by a 0.2ml saline flush.

Thereafter one group of six three day post portal vein ligation rats and one group of seven twenty-eight day post portal vein ligation rats had 4μg/kg/hr SMS 201-995 in saline infused at 0.05 ml/min via the femoral vein. The other two groups continued to have saline infused. After 30 minutes of infusion 0.1ml Sn-113 labelled microspheres (1000 microspheres) were vortexed for three minutes and injected into the portal vein cannula followed by a 0.2ml saline flush.

In the twenty-eight day post portal vein ligation groups the experiment was terminated two minutes after the second injection and the animal killed by intravenous injection of 1ml saturated potassium chloride. In the three day post portal vein ligation groups the experiment was continued for a further thirty minutes before sacrifice. Five ml blood samples for SMS 201-995 levels were taken from the femoral artery cannula immediately before sacrifice. After this the lungs and liver were removed and counted in a gamma scintillation counter as described for the previous experiment. Counting took place over five minutes per sample using an 80-150keV energy window for Co-57 and a 300-450keV window for Sn-113. Counts were corrected for spillover using Co-57 and Sn-113 standards. Two values for percentage portasystemic shunting were obtained for each rat, at 30

minutes and 60 minutes from the start of the experiment. Values for the systolic, diastolic, pulse, mean arterial and mean portal pressures for 0, 30, 60, 90 minutes were obtained as previously described.

The results were compared using Mann Whitney U tests to compare the change in portal and mean arterial pressures and change in %portasystemic shunting in the control and study groups for both the three day post portal vein ligation and the twenty-eight day post portal vein ligation rats. $p<0.05$ was taken as the level of statistical significance.

Results

The results for the three day post portal vein ligation rats are summarised in Table 18. No results were excluded from analysis. Appendix 6 shows the raw data for each rat. No significant difference in mean arterial pressure was seen between the control and study groups, throughout 60 minutes of infusion of saline or SMS 201-995 (from 30 to 90 minutes of the experimental period). In both groups there was a fall in portal pressure but there was no difference in this fall between the groups ($p=0.29$). As is seen in Figure 16 there was no consistent change in %portasystemic shunting in either control or study groups. There is no statistically significant difference between the groups ($p=0.32$). Both groups became increasingly acidotic throughout the experiment.

The results for the twenty eight day post portal vein ligation rats are shown in Table 19. Appendix 7 shows the raw data for each rat. The results from one rat given SMS 201-995 were excluded from the analysis because of a reduction of 40mmHg in mean arterial pressure due to bleeding from the mesentery around the portal vein cannula. There were no significant differences in mean arterial pressure between the control and study groups. The control group sustained a larger drop in portal pressure than the study group but this difference between the control and study groups was not significant ($p=0.07$). Changes in %portasystemic shunting were very variable in both groups.

There is no statistically significant difference between the groups ($p=0.31$).

When the results for both groups are considered there was no correlation between the drop in portal pressure with SMS 201-995 and initial portal pressure ($r=0.31$; $t=0.98$; Figure 17), initial %portasystemic shunting ($r=0.26$; $t=0.81$) or the change in %portasystemic shunting ($r=0.123$, $t=0.37$; Figure 18). Neither was there any correlation between the change in arterial pressure and change in portal pressure when all the groups were considered ($r=0.25$; $t=1.21$; Figure 19).

Plasma levels of SMS 201-995 were found to be <100pg/ml in all control group animals and >2500pg/ml in all study group animals.

Table 18 - The effect of 4μg/kg/hr SMS 201-995 on portal pressure and portasystemic shunting in 3 day post portal vein ligation rats. Results shown were measured at 30 and 60 minutes (before drug/saline and after 30min infusion). Arterial pressure is shown in mmHg, portal pressure in cm water and weight in grams. All values except pH are mean ± standard error. n=6 for each group.

		CONTROL GROUP	STUDY GROUP
WEIGHT		279.3±11.6	273.0±11.3
pH median(range)			
	30	7.27(7.23-7.3)	7.32(7.23-7.34)
	60	7.22(7.15-7.33)	7.27(7.2-7.34)
pCO	30	36.4±1.3	34.7±0.6
	60	36.3±1.2	38.1±1.4
BASE EXCESS	30	-9.7±1.0	-7.9±1.2
	60	-11.6±1.3	-8.1±1.6
MEAN ARTERIAL	30	89.7±7.9	99.4±6.7
	60	84.3±6.2	99.7±6.7
	90	82.4±13.2	90.7±6.8
MEAN PORTAL	30	17.5±1.4	14.6±1.9
	60	13.0+1.3	11.0±2.2
	90	10.4±1.5	9.2±2.4
%SHUNTING	30	43.1±12.4	57.3±12.6
	60	42.9±12.7	51.1±13.8

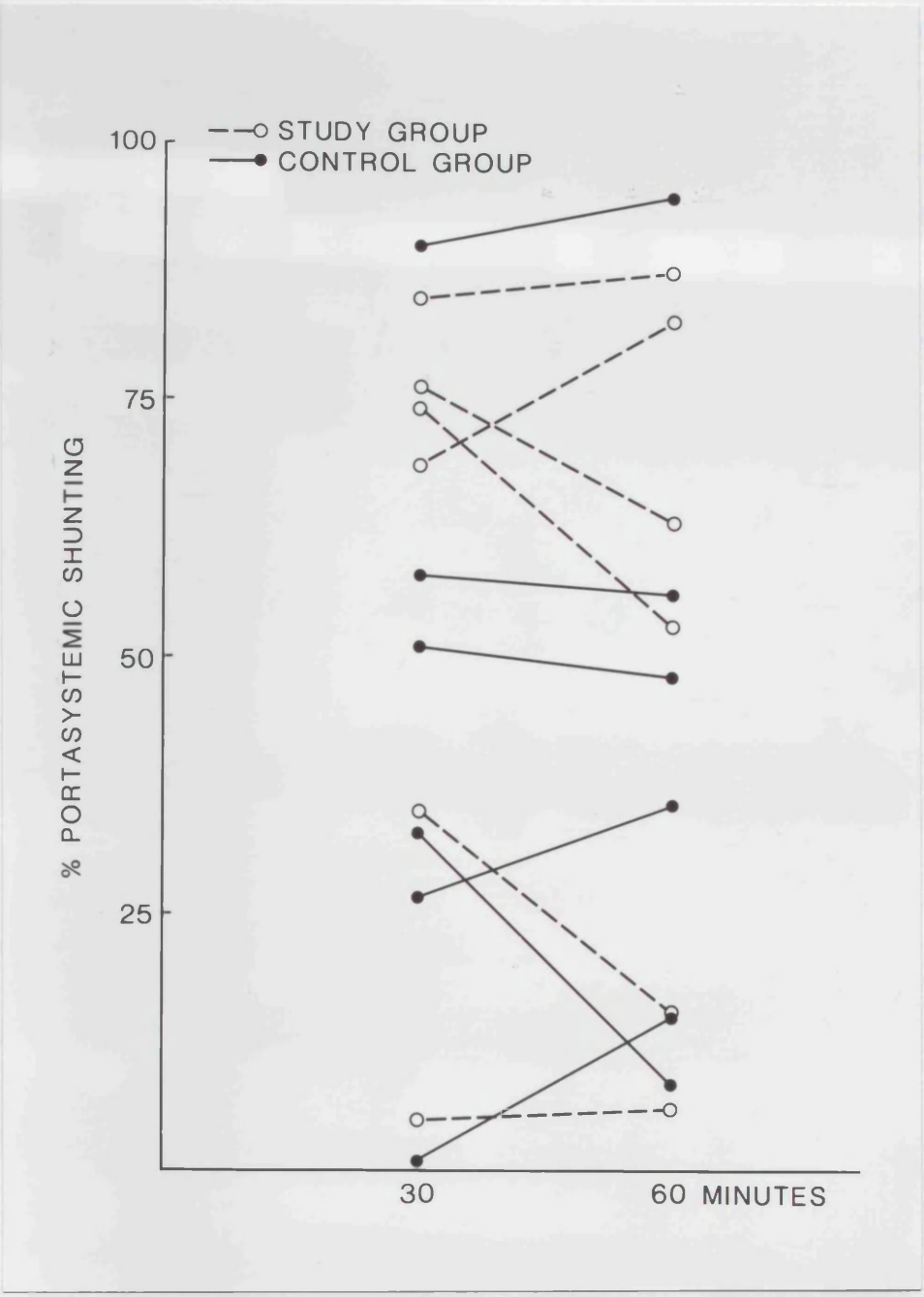

Figure 16 - %portasystemic shunting in twelve 3 days post portal vein ligation rats. Measurement before and after a 30 minute intravenous infusion of saline (6 rats) or 4µg/kg/hr SMS 201-995 (6 rats).

Table 19 - The effect of 4μg/kg/hr SMS 201-995 on portal pressure and portasystemic shunting in 28 day post portal vein ligation rats. Results shown were measured at 30 and 60 minutes (before drug/saline and after 30min infusion). Arterial pressure is shown in mmHg, portal pressure in cm water and weight in grams. All values are mean ± standard error. n=6 for control group, 5 for study group.

		CONTROL GROUP	STUDY GROUP
WEIGHT		364.5±20.6	364.4±8.9
pH median(range)			
	30	7.28(7.21-7.37)	7.26(7.25-7.3)
	60	7.22(7.15-7.31)	7.26(7.25-7.3)
pCO	30	36.9±2.2	33±2.2
	60	37.4±1.9	35±3.3
BASE EXCESS	30	-7.9±0.9	-8.1±1.6
	60	-12.1±1.1	-9.9±1.1
MEAN ARTERIAL	30	105.0±2.6	104.5±5.0
	60	99.1±5.2	110.2±9.2
MEAN PORTAL	30	11.3±0.8	9.9±1.0
	60	9.8±1.2	9.6±1.1
%SHUNTING	30	55.8±7.4	48.8±14.2
	60	58.9±10.4	51.9±10.7

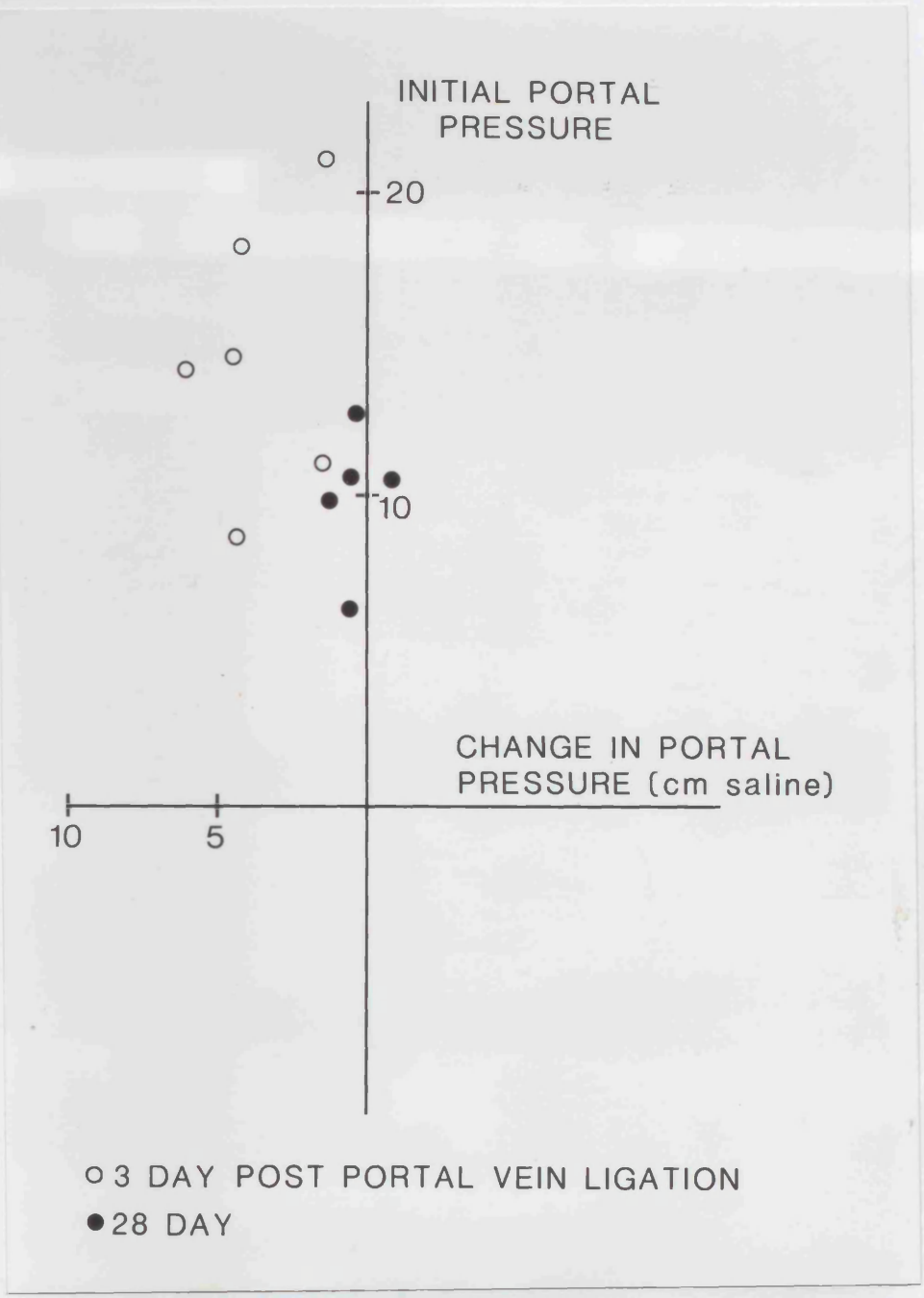

Figure 17 - Plot of change in portal pressure against initial portal pressure in eleven portal vein ligated rats (six 3 days and five 28 days post portal vein ligation rats) given an intravenous infusion 4µg/kg/hr SMS 201-995 for 30 minutes. $r=0.31$. $t=0.98$. $p<0.5$.

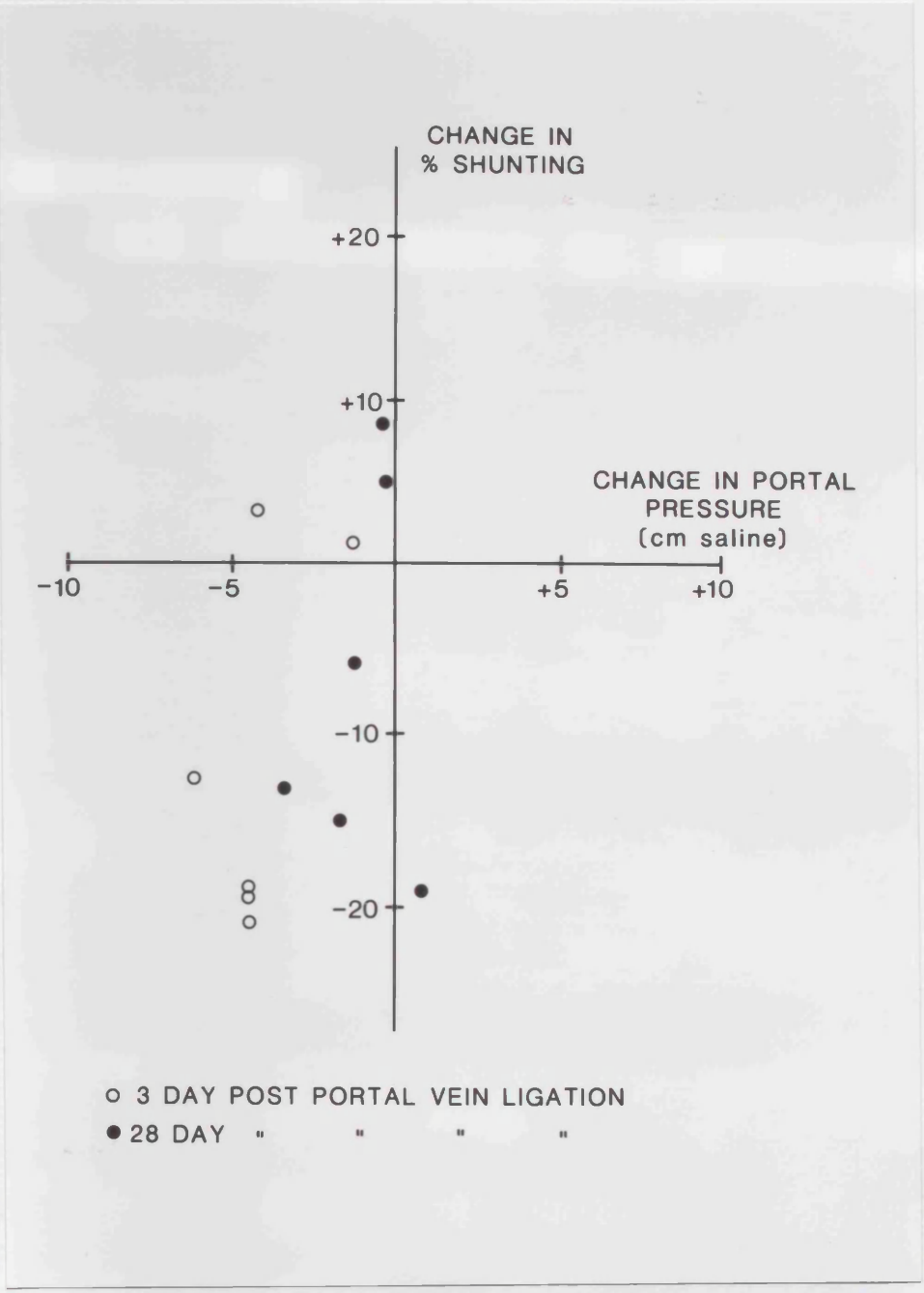

Figure 18 - Plot of change in portal pressure against change in %portasystemic shunting in portal vein ligated rats (six 3 days and five 28 days post portal vein ligation) given an intravenous infusion of 4µg/kg/hr SMS 201-995 for 30 minutes. r=0.12. t=0.37. p>0.5.

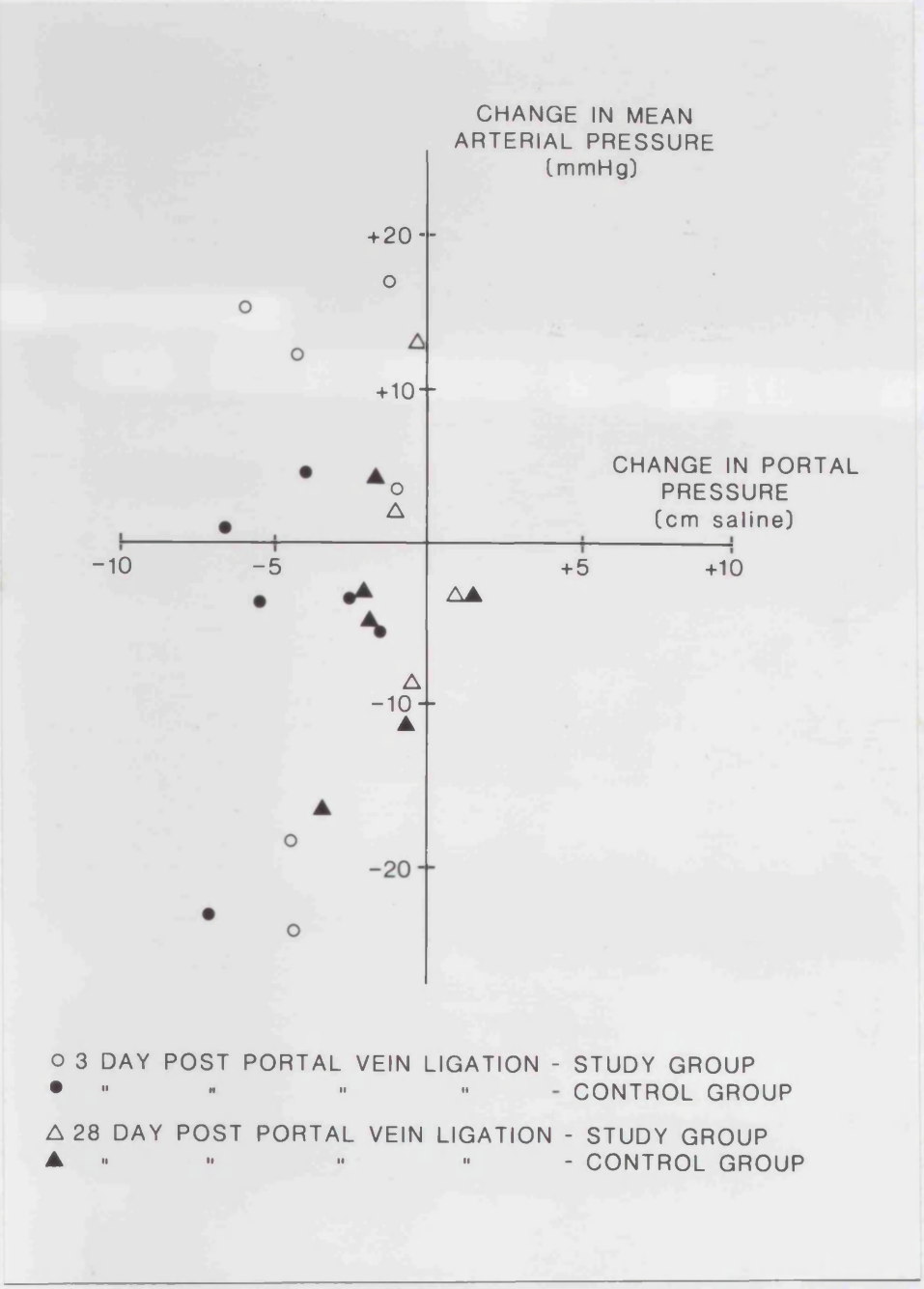

Figure 19 - Plot of change in portal pressure against change in mean arterial pressure in 23 rats in four groups - six 3 days post portal vein ligation given saline; six 3 days post portal vein ligation given 4μg/kg/hr SMS 201-995; six 28 days post portal vein ligation given saline; five 28 days post portal vein ligation given 4μg/kg/hr SMS 201-995. All infusions over 30 minutes. $r=0.25$. $t=1.21$. $p<0.5$.

Discussion

In this experiment no systemic haemodynamic changes were seen in either control or study groups. Portal pressure fell in all groups but no significant effects of SMS 201-995 could be shown. A wide variety of changes in shunting was seen.

In the part of this experiment using 3 day post portal vein ligation rats a longer time scale was used than in previous experiments. Because the problems due to blood loss and falling arterial and portal pressures had been most apparent at the beginning of the experiments, it was felt that a longer period following the insertion of the cannulas might allow the animals to stabilise. The drug infusion was also given in the highest dose for a longer period to minimise the chance that an effect was missed because of too short a period of observation. However during the course of these long experiments portal pressures fell slowly in both control and study groups and this often occurred with little or no blood loss. The calibration and base-line of the pressure transducers was checked regularly to ensure that this was not the cause of the change. The conclusion was that the slowly incresing metabolic acidosis in the animals might be responsible for the change in portal pressure. This was difficult to prevent although the changes were similar in the control and study groups.

In the 28 day post portal vein ligation rats similar negative results with SMS 201-995 were obtained, although

the drug infusion was not prolonged beyond thirty minutes.

As previously noted in this department (7), a wide range of %portasystemic shunting was produced by portal vein ligation. No consistent change in %portasystemic shunting was caused by the infusion of SMS 201-995 in these animals. This is perhaps not surprising since a wide variety of anatomy and degree of shunting is found before drug treatment. Haemodynamic changes must have been occurring in the control rats with time, despite the unchanged systemic arterial blood pressure, since they also sustained changes in %portasystemic shunting. Other influences such as acid-base balance must have been more important than any influence of SMS 201-995.

Throughout this experiment considerable variety in response was noted. In order to establish whether portal pressure response to SMS 201-995 is influenced by initial portal pressure, initial %portasystemic shunting or change in %portasystemic shunting, these variables were plotted for each animal (Figures 17 and 18) and the correlation coefficient calculated. No evidence of correlation between the change in portal pressure and the other variables was found. Since any change in portal pressure might be simply due to a change in arterial pressure these two variables were plotted (Figure 19). No simple correlation was found.

THE EFFECT OF SMS 201-995 ON PORTAL PRESSURE AND PORTASYSTEMIC SHUNTING IN CIRRHOTIC RATS.

Introduction

The aim of this experiment was to establish whether SMS 201-995 affects portal pressure and %portasystemic shunting in cirrhotic rats. Since these animals have abnormal liver function it was felt that they might react differently from animals with extrahepatic portal hypertension.

Materials and methods

Twenty male Sprague-Dawley rats, weighing between 295g and 455g were used in this experiment. Each of these rats had been treated with carbon tetrachloride to produce cirrhosis as described previously, and had evidence of ascites on examination. All experiments were performed between 7 and 14 days after the onset of ascites.

On the day of the experiment the rats were fasted for at least twelve hours before anaesthesia was induced in a perspex box with 2% halothane and a mixture of 2:1 nitrous oxide and oxygen. A tracheostomy was performed and the rat was then ventilated using a mixture of 2:1 nitrous oxide and oxygen and 0.5% halothane. A heating lamp was used to maintain rectal temperature between 36.5 and 37.5°C.

Laparotomy was performed via a lower midline incision and the ileocolic tributary of the portal vein cannulated to record portal pressure. The abdomen was closed in two layers with chromic catgut. One femoral artery was cannulated for arterial pressure recording. One femoral vein was cannulated for drug infusion. A minimal amount of heparinised saline (500 units sodium heparin in 500ml normal saline) was injected through the cannulae to prevent clotting. Blood gas estimations were performed before the infusion began. Then 0.1 ml Co-57 labelled microspheres (1000 microspheres) in 10% dextran was vortexed for 3 minutes then injected into the portal vein cannula followed by a 0.2ml saline flush.

Thereafter one group of eleven rats had 4µg/kg/hr SMS

201-995 in saline infused at 0.05 ml/min via the femoral vein. The other group of nine rats had saline infused at the same rate. After 20 minutes of infusion 0.1ml Gd-153 labelled microspheres (1000 microspheres) were vortexed for three minutes and injected into the portal vein cannula followed by a 0.2ml saline flush. Blood gas estimation was then repeated.

The experiment was terminated two minutes after the second injection and the animal killed by intravenous injection of 1ml saturated potassium chloride. Five ml blood samples were taken from the femoral artery cannula immediately before sacrifice for SMS 201-995 levels and liver function tests. A small liver biopsy was taken for histology. After this the lungs and liver were removed and counted in the gamma scintillation counter as described for the previous experiment. Counts were corrected for spillover using Co-57 and Gd-153 standards. Two values for percentage shunting were obtained for each rat, at time zero and twenty minutes after the start of the experiment. Values for the systolic, diastolic, pulse, mean arterial and mean portal pressures for 0, 30, 60, 90 minutes were obtained as previously described.

The results were compared using Mann Whitney U tests to compare the change in portal pressure and change in %portasystemic shunting between the study and control group. Results were considered significant if $p<0.05$.

Results

Two rats in the study group sustained a severe drop in arterial blood pressure because of bleeding after portal vein cannulation. Their results are not included in the analysis. The liver function tests and histology of these rats are shown in Table 20. The results of the haemodynamic studies are shown in Table 21. Appendix 8 shows the data for each rat studied. The blood gas results are less comparable in this experiment than the others, and the study group started with a lower pCO than the control group. The control group also became more acidotic during the experiment. There are no significant differences between the groups with regard to change in portal pressure ($p=0.33$) or %portasystemic shunting ($p=0.39$). Figure 20 demonstrates that a variety of changes in %portasystemic shunting was seen in both control and study groups.

SMS 201-995 levels at the end of the experiment were found to be <100pg/ml in all control group animals and >2500pg/ml in all study group animals.

Table 20 - Liver function tests in 18 cirrhotic rats used in the portal pressure and %portasystemic shunting experiment. ALT=Alanine transaminase, AST=Aspartate transaminase. All values are mean±standard error. Mann-Whitney U Tests show no significant differences between the groups.

LIVER FUNCTION TEST	CONTROL GROUP	STUDY GROUP	p
Number	9	9	
Bilirubin(μmol/l)	5±1	8±2	0.07
Albumin(g/l)	21±3	19±1	0.8
ALT(units/l)	83±19	155±55	0.3
AST(units/l)	284±34	433±128	0.3
Alkaline Phosphatase (units/l)	375±49	362±35	1.0

Table 21 - The effect of 4μg/kg/hr SMS 201-995 on portal pressure and portasystemic shunting in cirrhotic rats. Results shown were measured at zero and 20 minutes (before and after 20minutes of drug/saline infusion). Weight is shown in grams, arterial pressure in mmHg and portal pressure in cm water. All values are mean ± standard error. n=9 for each group.

		CONTROL GROUP	STUDY GROUP
WEIGHT		357.3±23.7	386.4±15.5
pH median(range)			
	0	7.34 (7.24-7.39)	7.30 (7.26-7.42)
	20	7.23 (7.1-7.32)	7.3 (7.23-7.42)
pCO	0	32.6±1.2	28.0±2.8
	20	31.8±1.5	31.1±2.2
BASE EXCESS	0	-7.9±1.0	-10.6±1.5
	20	-13.0±1.0	-8.5±2.6
MEAN ARTERIAL	0	89.2±4.3	90.8±4.9
	20	78.9±3.4	87.4±6.1
MEAN PORTAL	0	12.5±1.8	12.3±0.9
	20	11.4±1.7	11.6±1.1
%SHUNTING	0	18.6±4.5	15.0±4.6
	20	21.6±5.6	20.5±6.3

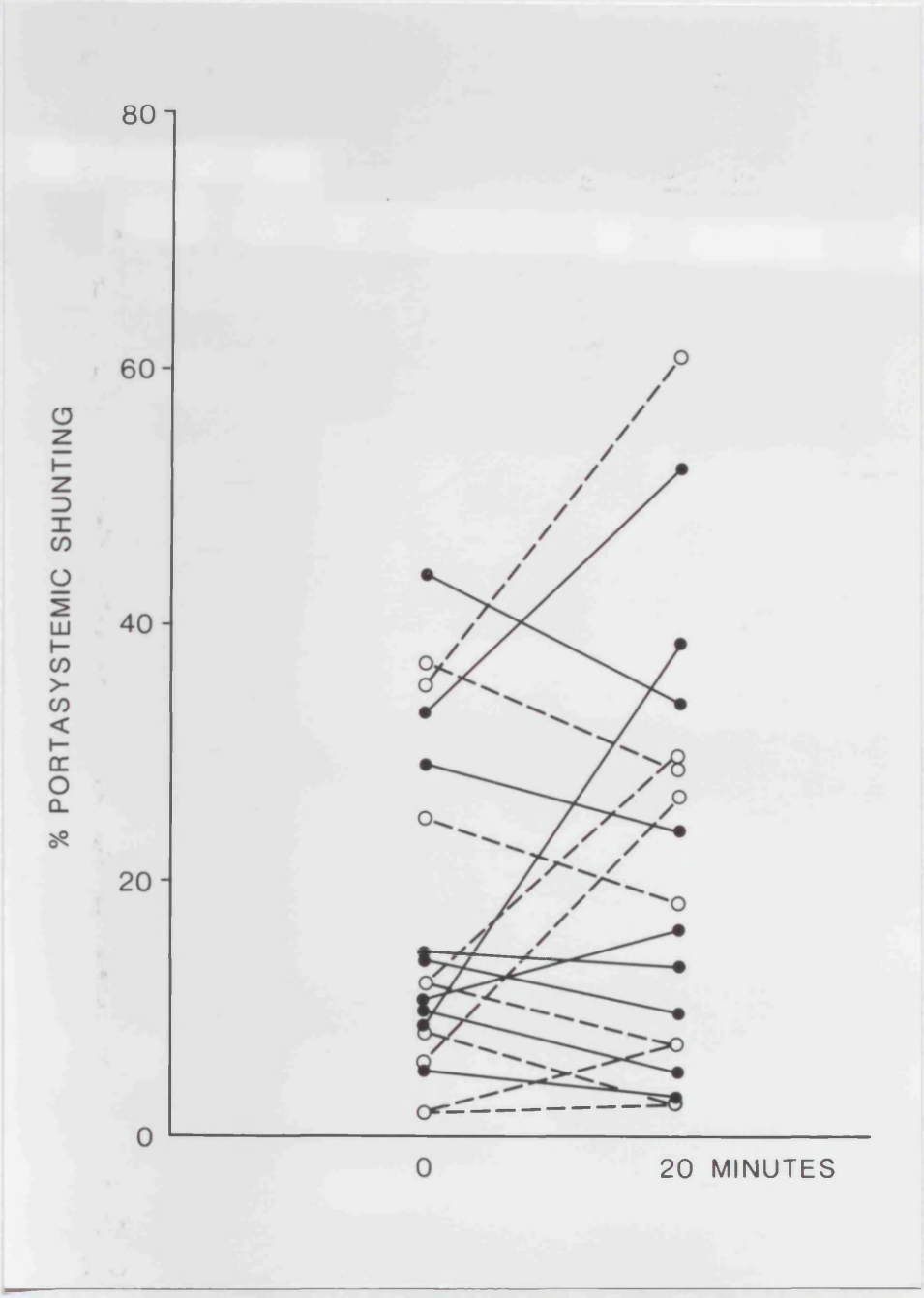

Figure 20 - %portasystemic shunting in ten cirrhotic rats measured before and after a 20 minute intravenous infusion of saline (9 rats) or 4µg/kg/hr SMS 201-995 (9 rats).

Discussion

The rats used in this experiment all had ascites, splenomegaly and histological and biochemical evidence of hepatic cirrhosis. It was felt that the combination of abnormal liver function and the arteriovenous and portasystemic shunts known to exist in cirrhosis (243) might well cause a different reaction to SMS 201-995 than in animals with extrahepatic portal hypertension. A shorter experimental and infusion time was chosen since prolonging the previous experiments had been of no obvious benefit. Despite this shorter drug infusion, adequate levels of SMS 201-995 were achieved.

This experiment showed no change in systemic blood pressure or portal pressure after SMS 201-995 infusion and no consistent change in %portasystemic shunting after SMS 201-995 infusion.

DISCUSSION

In conclusion, this series of experiments has shown that SMS 201-995 does not have significant systemic haemodynamic effects in rats. It has not been possible to demonstrate a significant reduction in portal pressure in normal rats, rats with extrahepatic portal hypertension or cirrhotic rats.

There are several possible explanations for the lack of effect of SMS 201-995 on portal pressure in these experiments. Firstly, the change in portal pressure may be small and thus difficult to demonstrate with small numbers of animals. However not even a trend towards a fall in portal pressure was seen. Secondly, the method of measuring portal pressure may not be sensitive enough, but differences in portal pressure between normal, portal vein ligated and cirrhotic rats have been shown which are consistent with previous work (7,131,203,230,244,245) and since the experiments reported here, reductions in portal venous pressure in cirrhotic rats given propranolol have been demonstrated (unpublished observations). Thirdly, the possibility that the effect of SMS 201-995 is being reduced because the preparation is actually a haemorrhaged-transfused model (242) has arisen. This may be the case in the first 3 day post portal vein ligation group but in the later experiments there was little evidence of haemorrhage in the rats used either during cannulation or

thereafter. Finally it may be that SMS 201-995 does not consistently cause a significant reduction in portal pressure in rats. Jenkins and colleagues (131), in rats made cirrhotic using dimethylnitrosamine and anaesthetised with pentobarbital, demonstrated a reduction in portal pressure after intravenous infusion of 1-4μg/kg/hr of SMS 201-995 for 20 minutes. Cerini et al (240) showed no significant reduction in portal pressure in normal rats but significant effects at higher doses in portal hypertensive rats. In 3 week post partial portal vein ligated rats a significant reduction in portal pressure was shown with doses of 4μg/kg/hr and above and in 4 week post bile duct ligated rats a significant reduction was shown with doses of 2 μg/kg/hr SMS 201-995. The measurements in Cerini and colleagues experiments were performed in unanaethetised animals.

The differences between these groups results and the results reported here may well be explained by differences in the models of portal hypertension used and by differences in anaesthesia. Bile duct ligation is a model of secondary biliary cirrhosis and causes jaundice (246). The reduced liver function in these rats compared to our carbon tetrachloride treated rats, only two of which had a plasma bilirubin greater than 30μmol/l, may have caused reduced metabolism of SMS 201-995 and thus increased any effect (247). The DMNA model of cirrhosis uses a known carcinogen as the agent causing hepatic damage and nodule formation was

not reported in all rats treated in a study by Jenkins et al (248), although portal hypertension developed with ascites. These differences in the models of cirrhosis may account for the differing results reported.

Previous work has shown that pentobarbital anaesthesia alters systemic and splanchnic haemodynamics in bile duct ligated rats(247). Pentobarbital also reduces circulatory responses to haemorrhage (249) and to beta-blockade (250). Haemodynamic differences between conscious and halothane anaesthetised rats have not been studied but it is possible that halothane has altered the response to SMS 201-995. It is therefore difficult to compare results of haemodynamic studies which have used different methods of anaesthesia and this may be another factor causing apparently contradictory results.

In summary, no clear evidence of a reduction in portal pressure or alteration in splanchnic haemodynamics due to SMS 201-995 has been demonstrated in our animal model. In view of this, further elucidation of the mode of action of SMS 201-995 in this model is clearly impractical.

CHAPTER 7

A COMPARISON OF THE EFFICACY OF SMS 201-995 AND OESOPHAGEAL TAMPONADE IN THE CONTROL OF ACUTE VARICEAL HAEMORRHAGE.

INTRODUCTION

Having established that SMS 201-995 causes a 30% reduction in portal pressure in a group of stable cirrhotic patients a controlled clinical trial was commenced to assess its efficacy in active variceal bleeding. Naturally occurring somatostatin has been compared to vasopressin for the control of variceal bleeding in two clinical trials (4,5) and was thought to be at least as effective as vasopressin but with less side-effects. However because of its instability in solution and its very short half-life, practical problems arise during its administration. Rebound phenomena have also been observed at the end of intravenous infusions of somatostatin (251). Since SMS 201-995 is a long-acting octapeptide with a half-life of 45 minutes in plasma it might well be a more useful drug. No rebound phenomena have been observed after SMS 201-995 infusion and its effect on insulin levels is small and short-lasting in comparison to its other effects (6).

In this clinical trial the results of treatment with SMS 201-995 have been compared with those of treatment with the Minnesota modification of the Sengstaken Blakemore tube. In the University Department of Surgery, Glasgow Royal Infirmary, oesophageal tamponade has been the standard means of control of active variceal bleeding for the past eight years. As reported in Chapter 2, a recent retrospective review of the results shows a 94% bleeding control rate in 126 bleeds from oesophageal varices with a 10% incidence of

chest infection as a complication. Although control of bleeding with oesophageal tamponade is good the incidence of complications is significant and the tube causes considerable discomfort to the patient. SMS 201-995 has not been associated with any significant side-effects in patients treated for acromegaly (252) or carcinoid syndrome (253). If control of variceal bleeding with SMS 201-995 is comparable to that achieved with tamponade then this drug might achieve a significant improvement in the management of variceal bleeding.

PATIENTS AND METHODS

Forty patients were included in the study. At entry all patients had endoscopy proven active bleeding from oesophageal varices, of such a degree as to require blood transfusion. Portal hypertensive patients with bleeding from other sources were excluded as were patients who had had a myocardial infarction within the last six months, patients with renal failure requiring dialysis and patients with insulin dependent diabetes mellitus.

Following admission to hospital with a suspected variceal bleed, patients were resuscitated with blood and plasma and fibreoptic endoscopy under sedation was performed within two hours. Prior to endoscopy the trial was explained and verbal consent obtained from either the patient or a relative. This study was approved by the Ethical Committee of the Royal Infirmary, Glasgow. Having confirmed active bleeding from oesophageal varices patients were randomised to treatment with SMS 201-995 or oesophageal tamponade using numbered sealed envelopes. The severity of the bleed was graded by the endoscopist as mild, moderate or severe depending on the endoscopic findings and the patient's clinical state on admission. The amount of blood transfused prior to endoscopy and the time from the start of overt bleeding was recorded. Patients treated with SMS 201-995 were given an intravenous infusion of 25ug/hr SMS 201-995 in 120ml normal saline over 48 hours via a syringe pump (Treonic IP4, Vickers Medical). Patients randomised to oesophageal tamponade had the

Minnesota modification of the Sengstaken Blakemore tube (4 lumen) passed through the mouth or nose by an experienced member of medical staff. The gastric balloon was inflated with 100ml of saline and 20ml of water-soluble contrast medium. The oesophageal balloon was inflated to 40mm Hg as indicated by an anaeroid barometer and the tube gently taped in place. The tube position was confirmed by chest X-ray immediately after insertion and the patient was constantly supervised by a trained nurse who aspirated the gastric and pharyngeal lumina of the tube hourly. Between aspirations the lumina remained on open drainage. The tube was left in place for 24 hours with both balloons inflated. At 24 hours the oesophageal balloon was deflated and the tube untaped so that the gastric balloon lay free in the stomach. If further bleeding occurred the oesophageal balloon was re-inflated and the tube taped as before. The tube was removed at 48 hours.

The standard general measures used to treat variceal bleeding were employed in all patients. Blood and plasma were used for volume and red cell replacement. Vitamin K, fresh frozen plasma, platelets and/or cryoprecipitate were given as appropriate if a coagulation defect was found at the time of the bleed. Oral lactulose and regular bowel washouts were used to try to prevent encephalopathy.

All patients were closely monitored with hourly blood pressure, pulse, urine volume and temperature measurements. Patients in the SMS 201-995 arm had a naso-gastric tube

passed to monitor gastric aspirations hourly.

At the end of the trial period all patients underwent a further fibreoptic endoscopy under sedation to assess control of bleeding and to perform injection sclerotherapy.

All patients had clinical examination and the following investigations performed at 0 and 48 hours: full blood count, coagulation screen, urea and electrolytes, random glucose, liver function tests, plasma proteins, gamma-glutamyl transferase, urate, cholesterol and arterial blood gases. An electrocardiogram and chest X-ray were performed at the beginning and end of the 48 hour period. Pugh's modification of Child's grading was assessed at 0 and 48 hours for each patient. In addition, full blood count and serum glucose were repeated 12 hourly and urea and electrolytes and liver function tests repeated at 24 hours. Two successive creatinine clearance measurements were also performed. Clinical examination, chest X-ray and arterial blood gases were repeated at 72 hours and 7 days from admission to the trial. Fluid balance and requirements for blood and blood products were recorded, along with pulse and blood pressure measurements at 12 hourly intervals.

Cessation of bleeding was recorded at the hour when less than 20ml of fresh blood was aspirated from the stomach provided there was no other evidence of bleeding. Rebleeding was deemed to have occurred if one or more of the following criteria were fulfilled:

a) overt haemorrhage or aspiration of more than 100ml fresh

blood.

b) passage of fresh blood per rectum

c) fall in haemoglobin concentration of more than 4g/dl within 48 hours

d) shock (pulse rate>100:systolic blood pressure<100) in the presence of continuing melaena.

If either treatment failed to control the bleeding or if rebleeding occurred during the 48 hours of treatment the patient was crossed over to the other treatment. Control of bleeding was assessed during the first 4 hours of the trial period (recorded as initial control) and for the whole 48 hour period (complete control). The further progress of the patient during that admission to hospital was recorded, with particular regard to survival and cause of death. Symptomatic side-effects were assessed by enquiry from the patient and nursing staff. Evidence of chest infection was looked for carefully by means of clinical examination, serial chest X-rays and blood gases and was deemed to be present if any of these parameters became abnormal, consistent with a chest infection. Other complications were recorded as they arose.

Comparisons of the two groups with regard to age, preadmission blood transfusion, time to bleeding control, amount of blood transfused and creatinine clearance values were carried out using the student's t-test. Comparisons of the distribution of sex, aetiology, modified Child's grading, number of patients who had pre-admission blood

transfusion, number of first bleeds and control rate at 48 hours were performed using Chi-squared tests.

Bleeding control rate at four hours, number of rebleeds, number of crossovers and survival were compared using Fischer's exact test. $p<0.05$ was taken as the level of statistical significance.

RESULTS

The results of this trial are summarised in Appendices 9 and 10. 40 episodes of endoscopically proven active variceal bleeding were included. Over the 23 months during which the trial was running (1/7/86 - 31/5/88) 56 bleeds in 41 patients were excluded. On each of these occasions a patient was admitted within 48 hours of haematemesis or melaena which was thought to have been from oesophageal varices. The reasons for exclusion from the trial are shown in Table 22. 13 of these excluded bleeds proved fatal, either due to the bleed itself or its complications.

40 bleeds in 31 patients were included in the trial. 20 bleeds were randomised to oesophageal tamponade and 20 bleeds were randomised to treatment with SMS 201-995 infusion. These two groups were comparable with regard to sex ratio, age and aetiology of portal hypertension (Table 23), and though the oesophageal tamponade group had more modified Child's C grade patients than the SMS 201-995 group, this difference was not statistically significant($p<0.3$).

The characteristics of the variceal bleeds included in this trial in terms of the number of first bleeds from varices, the estimated severity of the bleed, the time from its initial manifestation and the amount of blood transfusion given before admission to the trial were similar in the two groups, as shown in Table 24.

Control of bleeding

Bleeding was controlled over the first four hours after admission to the trial in 19 of 20 patients treated with oesophageal tamponade and 18 of 20 patients treated with SMS 201-995 infusion. This difference is not statistically significant ($p<1.0$). The bleed not controlled by tamponade was crossed over to SMS 201-995 infusion at two hours but this also failed to control the bleeding. It was controlled by injection sclerotherapy but the patient died of hepatorenal failure at 40 hours from admission to the trial. This patient had a very poor prognosis on admission, having Grade III encephalopathy and a prothrombin time of 40 seconds (72). The two bleeds not controlled by SMS 201-995 infusion during the first four hours were crossed over to oesophageal tamponade, which controlled the bleeding.

In 15 bleeds oesophageal tamponade controlled the bleeding immediately (Appendix 9) although small amounts of fresh blood were aspirated from the stomach for several hours in four bleeds. In 11 bleeds SMS 201-995 infusion controlled the bleeding within the first hour with seven bleeds taking longer to settle (Appendix 10). This difference in time to control of bleeding is not statistically significant ($p<0.34$).

Over the 48 hour trial period, two patients in the oesophageal tamponade group died, the patient mentioned above whose bleeding was uncontrolled by tamponade and SMS 201-995 infusion, and one other patient who died at 4.5

hours from admission due to hepatorenal failure. In 14 of the other 18 bleeds in the oesophageal tamponade group there was no rebleeding over this time. In two bleeds rebleeding occurred during the first 24 hours when the oesophageal balloon should have been inflated, but in one case this had been accidentally deflated and in the other the oesophageal balloon had burst, despite once only use. Two other rebleeds occurred during the second 24 hours when the oesophageal balloon was deflated. All four of these rebleeds were easily controlled by either re-inflation of the oesophageal balloon or the insertion of a new Minnesota tube in the case where the balloon had burst. Therefore no bleed required crossover to SMS 201-995 infusion because of rebleeding. In the SMS 201-995 group there was no rebleeding in 10 bleeds. In eight bleeds there was evidence of rebleeding but in four cases this settled without treatment. Four bleeds required crossover to oesophageal tamponade and the bleeding was controlled by this in each case. The difference in 48 hour bleeding control rate is not statistically significant ($p<0.1$).

The 20 bleeds in the oesophageal tamponade group required a mean of 1680mls (sem 295mls) of blood transfusion over the trial period while the 20 bleeds in the SMS 201-995 group required a mean of 1710mls (sem 252mls). There is no statistically significant difference between the groups ($p=0.4$).

Complications

In the total of 21 bleeds treated with SMS 201-995 infusion, no patient complained of any symptomatic side-effects. One patient who was a maturity onset diabetic required an intravenous infusion of soluble insulin 1-2 units/hour to maintain his plasma glucose at less than 15mmol/l but this controlled the plasma glucose level which remained stable when the SMS 201-995 infusion was stopped. No other patient required insulin infusion despite the fact that two other bleeds in the SMS 201-995 group occurred in maturity onset diabetics.

In 15 of the bleeds treated with oesophageal tamponade two creatinine clearance estimations were made. The mean of the mean creatinine clearance values for these patients was 106 ml/min(sem 10). The mean creatinine clearance rate in 16 patients treated with SMS 201-995 infusion was 84 ml/min(sem 9). The values for the two groups are not significantly different($p<0.5$).

Chest infection developed after 17 of the 39 bleeds evaluable. The patient who died at 4.5 hours has not been included in this consideration. The details of treatment and the incidence of uncontrolled of recurrent bleeding in these cases are shown in Table 25. There is a significant association between chest infection and rebleeding ($p<0.05$) but no association between chest infection and treatment with oesophageal tamponade ($p<0.3$). In the seven bleeds

where chest infection only developed after the second endoscopy, four endoscopies had been performed with the rigid oesophagoscope, giving an incidence of four chest infections developing in seven previously non-infected patients compared to three chest infections developing after 21 fibreoptic second endoscopies in non-infected patients. This difference is significant ($p=0.043$).

In the 26 bleeds treated at some time by oesophageal tamponade, 22 patients complained of discomfort caused by the Minnesota tube. All of the other four patients had hepatic encephalopathy.

Survival

None of the 20 bleeds in the SMS 201-995 group proved fatal, in comparison with five deaths from the 20 bleeds in the oesophageal tamponade group. This difference just reaches statistical significance ($p=0.047$).

Table 22 - The reasons for exclusion from the trial of 56 other bleeds thought to be from oesophageal varices.

No active bleeding after admission	31
Transfer from another hospital with Minnesota tube in place	11
Danger of exsanguination - tamponade instituted before endoscopy possible	5
Moribund on admission and could not be resuscitated	2
Wrong initial diagnosis of Mallory-Weiss tear	1
No active treatment - terminal disease	4
Emergency injection sclerotherapy	1
Excluded in error because of age	1
Total	56

Table 23 - Patient characteristics for the two groups treated with oesophageal tamponade or SMS 201-995 infusion for active variceal bleeding.

	OESOPHAGEAL TAMPONADE	SMS 201-995 INFUSION	p
Sex ratio (M:F)	16:4	18:2	>0.5
Age (mean±sem)	51.6±3.3	49.9±3.5	<0.7
Aetiology			
Alcoholic cirrhosis	13	15	
Primary biliary cirrhosis	1	1	
Chronic active Hepatitis	3	0	
Cryptogenic cirrhosis	3	1	<0.5
Sclerosing cholangitis	0	1	
Drug induced cirrhosis	0	1	
Congenital hepatic fibrosis	0	1	
Pugh's modification of Child's grade			
A	1	2	
B	4	8	<0.3
C	15	10	

Table 24 - Characteristics of the bleed for the two groups treated with oesophageal tamponade or SMS 201-995 infusion for active variceal bleeding.

	OESOPHAGEAL TAMPONADE	SMS 201-995 INFUSION	p
Number of first bleeds	6	9	<0.3
Severity			
Mild	13	11	
Moderate	4	7	<0.6
Severe	3	2	
Hours from start of overt bleeding (mean±sem)	20.5±4.2	17.9±3.6	<0.6
Number of patients transfused before admission to trial	11	9	<0.5
Mls of blood transfused per patient transfused before admission to study (mean±sem)	1464±308	1867±291	<0.6

Table 25 - Incidence of chest infections in comparison with type of treatment and occurrence of rebleeding.

	CHEST INFECTION	TOTAL NUMBER OF PATIENTS IN GROUP
SMS 201-995 infusion-total group	7	20
Oesophageal tamponade-total group	10	19
SMS 201-995 infusion alone	4	14
SMS 201-995 and tamponade	4	7
Oesophageal tamponade alone	9	18
Uncontrolled bleeding or rebleeding	10	15
No further bleeding	7	24

DISCUSSION

In this trial a 25μg/hr intravenous infusion of SMS 201-995 controlled bleeding during the first four hours of treatment in 18 of 20 patients with actively bleeding oesophageal varices. However the control rate had fallen to 50% by 48 hours. Oesophageal tamponade was able to control more bleeds without crossover, although this difference did not reach statistical significance.

The bleeds included in this trial formed 42% of all variceal bleeds treated in the unit while the study was ongoing. Since five patients with exsanguinating haemorrhage were treated with tamponade in the Accident and Emergency Department and two other patients with very severe bleeds could not be resuscitated on arrival in the ward, the patients with extremely severe bleeds may have been missed. On the other hand 31 patients who were admitted with a history of haematemesis and/or melaena but who had no active bleeding at endoscopy or recurrence of bleeding in hospital were also excluded. These latter patients represent the mildest variceal bleeds.

Because of the exclusion of the seven patients with very severe bleeds, four patients in whom no active treatment was felt to be appropriate and eleven patients transferred after initial treatment elsewhere who might also form a higher risk group, the mortality rate for the 40 bleeds included was lower (12.5% of bleeds) than the overall mortality rate of 18.7%. The fact that the most severe bleeds had a

tendency to exclude themselves from this trial is worth consideration since it implies that although drug treatment for variceal bleeding may become the preferred means of initial treatment, a number of very severe bleeds may still require tamponade. This has implications in terms of availability of the skilled staff and the equipment necessary for good results with oesophageal tamponade (83).

Two previous controlled clinical trials have compared the narurally occurring tetradecapeptide somatostatin with vasopressin in variceal bleeding. Kravetz et al (4) randomised 61 cirrhotic patients with variceal bleeding to 48 hours of treatment with a varying dose of vasopressin by intravenous infusion (starting at 0.4 units/min) or a bolus injection of 50µg of somatostatin followed by an intravenous infusion of 250µg/hr, rising to 500µg/hr if necessary. Patients who continued to bleed were withdrawn from the trial. 23 of 31 patients' bleeds were initially controlled by vasopressin but this had reduced to 18 of 31 at 48 hours. 26 of 30 patients' bleeds were initially controlled by somatostatin but this had fallen to 16 of 30 bleeds by 48 hours. Jenkins et al (5) entered 22 patients into their randomised controlled clinical trial comparing reducing doses of vasopressin by intravenous infusion or a 250µg bolus injection followed by an intravenous infusion of 250µg/hr of somatostatin over 24 hours. This study was similar to that of Kravetz and colleagues in that patients who continued to bleed were withdrawn. Bleeding was

controlled over 24 hours in all 10 patients treated with somatostatin but in only 4 of 12 patients treated with vasopressin.

The results of the present study with regard to bleeding control using SMS 201-995 are therefore similar to the results of Kravetz et al(4), though inferior to those of the Liverpool group (5). Since we have shown a deterioration in control of bleeding with time, the difference in results may be due to the longer trial period in both Kravetz and colleagues' study and the present study. In Jenkins et al's study somatostatin was only given to ten patients and the small numbers in the various studies may give rise to spurious differences.

The practical benefits of the longer acting analogue used in the present study lie in its greater stability in solution and longer half-life, which reduce the difficulties of intravenous infusion. From the study of the effects of SMS 201-995 on portal pressure in stable cirrhotics (Chapter 3) it is known that after a 60 minute infusion of SMS 201-995, transhepatic venous gradient is significantly reduced. If this reduction is sufficient to be of clinical importance in stopping variceal haemorrhage, haemorrhage should cease within the first few hours of infusion. 11 of the 18 bleeds controlled by SMS 201-995 stopped within the first hour. The cause of the recurrent bleeding during SMS 201-995 infusion might be tachyphylaxis to the treatment. Tachyphylaxis has been described for vasopressin (254) and

an early synthetic analogue of vasopressin, octapressin (255) and it has been suggested (242) that it occurs because of desensitisation of vasopressin receptors induced by the endogenous vasopressin secreted in response to haemorrhage. Because of the changes which are seen in splanchnic haemodynamics after significant haemorrhage, it may be that tachyphylaxis to somatostatin and its analogues also occurs. No rebound phenomena, such as recurrence of variceal haemorrhage after stopping somatostatin infusion, were observed in our patients, but it is possible that these effects were disguised by the effect of sclerotherapy in controlling bleeding. No disturbance of blood glucose levels was found.

A new treatment for any illness can be compared with either placebo or the current best means of treatment. It was felt that a comparison between SMS 201-995 and placebo was not justified on ethical grounds and a comparison with the previous best means of treatment in our department has therefore been made. Previous controlled trials in variceal bleeding have achieved variable control rates with placebo - ranging from 25% at 24 hours (2), through 37% at 8 hours (77) to 45% at 24 hours (88). However strict comparison of trials is difficult because of differences in the severity of bleeds included, in the accuracy of diagnosis, in the means of conservative treatment, in the length of time of the trial period and in the methods used to assess the results.

In Chapter 2 it was shown that oesophageal tamponade achieved control of bleeding in 94% of patients treated in the University Department of Surgery, Glasgow Royal Infirmary. Stricter criteria of control were used in the current prospective trial in which the oesophageal balloon was deflated during the second 24 hours of treatment in the tamponade group. This resulted in a lower control rate of 78% with tamponade at 48 hours, although control could be easily regained by reinflation of the oesophageal balloon. The initial bleeding control rate with tamponade remains high, and it is matched by a high initial bleeding control rate with SMS 201-995 infusion.

Although oesophageal tamponade has proved an effective means of control of variceal bleeding in the past, it has several potential serious side-effects and a comparison of the incidence of side-effects in the two groups in this trial is of considerable importance. Despite the fact that somatostatin plays a role in blocking both insulin and glucagon release at physiological levels (114) only one patient developed an abnormality of glucose homeostasis during SMS 201-995 infusion and this was controlled easily. Vora et al (130) has reported a reduction in renal function due to somatostatin. In patients with portal hypertension and actively bleeding varices many factors can influence a relatively simple measurement of renal function such as creatinine clearance but there was no difference in creatinine clearance rates in the two groups of patients.

Furthermore, no patient posed clinical problems with renal function while receiving an infusion of SMS 201-995.

Previous reports regarding the use of oesophageal tamponade have emphasised the risk of chest complications with this treatment. Novis et al (69) noted eight chest infections in 40 bleeds while Conn et al (82) reported eight cases of aspiration and one case of respiratory obstruction in 40 bleeds. If this incidence of chest infection was associated with tamponade alone, a reduction in this complication would have been expected in the group of patients treated with SMS 201-995 infusion only. This study has shown (Table 25) that chest infection was associated significantly with rebleeding or continued bleeding but not with tamponade. Furthermore, the use of the rigid oesophagoscope for injection sclerotherapy appearred to increase the risk of the patient developing a chest infection. The finding that oesophageal tamponade was not associated with an increased risk of chest infection is initially surprising in view of the previous reports of this complication (82,211,69,1). However in these severely ill patients there are a number of factors which might increase the risk of chest infection. Vomiting, endoscopic procedures, sedation and encephalopathy might all be to blame and these are difficult to separate in a study with relatively few patients.

In the present study, discomfort from the Minnesota tube was a major complaint in 22 of the 26 patients treated with tamponade and this dislike of tamponade contrasted markedly

with the lack of symptomatic side-effects in patients treated only with SMS 201-995 infusion. It is also worth considering that the administration of a drug infusion requires less expertise on the part of the nursing and medical staff than oesophageal tamponade. This may be a significant advantage in hospitals where relatively few patients with bleeding varices are seen and an SMS 201-995 infusion may buy time for the patient's safe transfer to a specialised centre.

The main aim of this trial was to assess the effect of SMS 201-995 on bleeding from oesophageal varices and the finding of a higher survival rate in the SMS 201-995 treated group of patients was unexpected. There was a higher number of patients with poor liver function in the tamponade group and although this difference in the modified Child's grading was not statistically significant both the non-significance of the difference in Child's grade and the significance of the difference in survival may be artefactual due to the small numbers. However this area merits further investigation since liver function is well established as the main influence of survival (148) after variceal bleeds and SMS 201-995 has been reported to improve the function of various organs in animals. It has been reported that naturally occurring somatostatin may have cytoprotective properties and prevent the development of hepatic and gastric lesions in rats (256). It was reported also to stimulate the reticulo-endothelial system in rats (257). Work from

Liverpool has shown that SMS 201-995 also stimulates the reticuloendothelial system in rats (133) and reduces the effects of endotoxaemia in rats (134). Work on the human reticulo-endothelial system with somatostatin or its analogue has not been published. However there is a possibility that such an effect on the reticulo-endothelial system might lead to improved survival since it is known that the reticulo-endothelial system is abnormal in liver disease (258).

In conclusion, infusion of SMS 201-995 would appear to have certain advantages over oesophageal tamponade for the immediate control of bleeding oesophageal varices, with any reduction in bleeding control being offset by its better tolerability. However, control deteriorates with time and it is possible that its future role may be in the temporary control of bleeding while the patient is resuscitated before acute injection sclerotherapy is undertaken.

CHAPTER 8

CONCLUSIONS

An episode of bleeding from oesophageal varices has a mortality rate of between 25 and 50% (69,60). Patients die not only because of inability to control bleeding but because of complications of the bleed or its treatment. Hepatic failure is a major cause of death and is the most difficult complication to deal with. It is worth noting, therefore, that control of variceal bleeding is only part of the management of patients with portal hypertension.

The methods of control of variceal bleeding currently in use vary in their efficacy and in their side-effects. No method is ideal.

Review of the literature reveals that it is possible to control over 90% of variceal bleeds using oesophageal tamponade (1) but this control is temporary. Some workers have found a high incidence of complications (82), and this is thought to occur particularly when tamponade is used by the inexperienced (83). Although vasopressin is widely used its major cardiovascular side-effects are well known (3) and doubts about its efficacy have been raised (89). The combination of vasopressin and vasodilators to try to reduce side-effects is not yet well established in clinical practice, and the long-acting triglycl vasopressin has similar cardiac side-effects to the original analogue (105). Despite the fact that naturally occurring somatostatin has been shown to be at least as effective as vasopressin in control of variceal bleeding (4,5) its short plasma half-life and instability in solution lead to practical

problems during the treatment of patients. Acute injection sclerotherapy has the advantage of providing definitive treatment and control rates of more than 80% have been reported by Terblanche (139). However sclerotherapy is technically difficult in the presence of active bleeding.

This thesis therefore set out to examine oesophageal tamponade as one of the current means of control and then to assess the long-acting somatostatin analogue SMS 201-995 with regard to its use in portal hypertension.

A retrospective review established that in the University Department of Surgery, Glasgow Royal Infirmary, 92% of variceal bleeds can be initially controlled by oesophageal tamponade. Although it was found that complications were strongly associated with poor liver function, a significant incidence of serious complications was recorded and the need for a better method of managing acute variceal bleeding was confirmed.

In stable cirrhotic patients, an intravenous infusion of 25ug/hr SMS 201-995 has been shown to cause a 30% reduction in transhepatic venous gradient with no effect on systemic haemodynamics and no significant side-effects. These results led on to the study of the effects of SMS 201-995 in animal models of portal hypertension and also formed the basis of the subsequent studies in actively bleeding patients.

The results of the animal work using SMS 201-995 were disappointing. No convincing reduction in portal pressure due to SMS 201-995 could be demonstrated in normal rats,

rats with extrahepatic portal hypertension or cirrhotic rats. Since differences in portal pressure between normal rats and the rat models have been demonstrated and drug effects have been shown using other compounds, it is concluded that in these animal models, anaesthetised with halothane, any effect of SMS 201-995 on portal pressure is minimal.

In the controlled trial comparing SMS 201-995 with oesophageal tamponade in active variceal bleeding, an initial control rate of 90% with SMS 201-995 was found in comparison to 95% with oesophageal tamponade. This control rate fell off to 70% at 24 hours and 50% at 48 hours compared to 84% at 24 hours and 77% at 48 hours with oesophageal tamponade. All the bleeds which were uncontrolled or where rebleeding occurred with SMS 201-995 were controlled by oesophageal tamponade. SMS 201-995 therefore probably gives a better bleeding control rate than might be expected with placebo (30% at 6 hours-Fogel, 1982(89); 37%-Freeman,1986(78)) and there is no statistically significant difference in the bleeding control rate between the groups treated with SMS 201-995 and oesophageal tamponade. The main advantage of SMS 201-995 treatment in comparison with oesophageal tamponade in actively bleeding varices was its tolerability to the patient. All conscious patients found that oesophageal tamponade produced considerable discomfort while no symptoms were reported by the patients treated with SMS 201-995

infusion. Chest complications were more strongly related to rebleeding episodes than to the means of treatment. This trial shows that SMS 201-995 may be useful in achieving initial control of bleeding, enabling resuscitation of the patient before injection sclerotherapy is performed as an urgent procedure. If bleeding can be controlled with SMS 201-995 infusion injection sclerotherapy will be technically easier and this should provide more definitive control of bleeding than is possible with drug infusion or oesophageal tamponade alone.

This work has suggested several further lines of investigation. The treatment of acute variceal bleeds with SMS 201-995 infusion followed by urgent sclerotherapy needs assessment in comparison with acute sclerotherapy alone or tamponade followed by acute sclerotherapy. Further investigation of the mode of action of SMS 201-995 is appropriate. Since animal work has not been helpful, possible methods for studying this in man should be examined. Control of bleeding varices is likely to be more closely related to the pressure in or flow through the varices themselves rather than to indirect measurements such as transhepatic venous gradient. Since the direct measurement of intravariceal pressure is now possible (259,260,261) and endoscopic Doppler flow probes have also been developed to measure variceal flow non-invasively (262,53) it would be useful to know the effect of SMS 201-995 infusion on variceal pressure and flow. The

measurement of azygos vein blood flow might also be a more relevant measurement than transhepatic venous gradient, since this will give a measure of the flow in at least some of the portasystemic shunts. This measurement is now possible using thermodilution techniques and specially shaped catheters (263).

The development of an oral analogue of SMS 201-995 is underway and once this is available further areas of use may be opened up. If it can be shown that long-term oral SMS 201-995 causes a reduction in either portal pressure or one of the more specific shunt blood flow parameters discussed above then a controlled trial of its efficacy in prevention of rebleeding from oesophageal varices will be worthwhile.

Our finding of an increased survival rate in patients with acute variceal bleeding treated with SMS 201-995 deserves further investigation. It has been suggested that SMS 201-995 stimulates the reticuloendothelial system (133) and affords protection from the effects of endotoxaemia (134). Patients with decompensated cirrhosis are known to have an increased risk of bacterial infections because of reduced reticuloendothelial function (258) and low serum fibronectin levels have been shown to be associated with a poor prognosis in cirrhotic patients (264). Thus SMS 201-995 may benefit the portal hypertensive patient in other ways than simply the reduction of portal or variceal pressure.

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APPENDIX 1

Individual patient data for wedged hepatic venous pressure and transhepatic venous gradient with and without an intravenous infusion of 25μg SMS 201-995 from 0 to 60 minutes. Pressures shown in mmHg.

CONTROL GROUP

	Wedged hepatic venous pressure				Transhepatic venous gradient			
Patient	0	60	120	180	0	60	120	180mins
JB	15	15	16	17	9	9	8	9
JT	13	13	14	13	11	11	11	10
WR	11	12	13	15	4	4	4	5
RM	13	14	15	14	8	8	9	8
PL	14	16	14	17	8	10	8	9
DO	18	18	22	25	4	6	8	11
TM	20	*	*	*	18	*	*	*
MEAN	14.8	14.6	15.6	16.8	8.8	7.8	8.0	8.6
SEM	1.4	1.1	1.6	2.9	2.1	1.3	1.1	1.0

SMS 201-995 GROUP

	Wedged hepatic venous pressure				Transhepatic venous gradient			
Patient	0	60	120	180	0	60	120	180mins
RS	14	12	12	14	9	8	8	9
AG	20	18	*	*	13	10	*	*
FW	16	14	14	16	12	10	12	13
JL	24	18	19	19	16	12	13	12
AA	19	10	18	19	19	10	15	17
AS	13	14	*	*	7	6	*	*
BB	24	20	24	28	21	18	22	23
AF	21	12	24	19	16	5	18	13
TM	19	15	18	19	14	10	15	14
MEAN	18.9	14.7	18.5	19.1	14.1	9.9	14.7	14.5
SEM	1.5	1.3	2.0	2.0	1.7	1.4	2.0	2.0

* missing value due to technical problems with equipment.

APPENDIX 2

Individual patient data for cardiac index and systemic vascular resistance with and without an intravenous infusion of 25ug SMS 201-995 from 0 to 60 minutes. Cardiac index shown in $l/min/m^2$, systemic vascular resistance shown in $dynes/s/cm^5$.

CONTROL GROUP

	Cardiac index				Systemic vascular resistance			
Patient	0	60	120	180	0	60	120	180
JB	4.3	3.2	3.6	3.9	949	1186	943	893
JT	5.4	3.8	3.6	3.6	994	1391	1336	1360
WR	4.4	3.3	3.4	3.5	759	951	917	940
RM	5.9	4.6	5.2	5.5	715	908	808	835
PL	4.8	4.1	4.7	4.4	867	997	896	872
DO	3.4	3.2	3.1	3.7	919	905	987	857
TM	3.5	3.0	*	*	992	1174	*	*
MEAN	4.5	3.6	3.9	4.1	885	1073	981	959
SEM	0.35	0.22	0.33	0.31	42	69	75	81

SMS 201-995 GROUP

	Cardiac index				Systemic vascular resistance			
Patient	0	60	120	180	0	60	120	180
RS	3.4	2.4	3.0	2.9	953	1357	1025	1236
AG	5.0	4.0	3.9	4.5	731	900	829	786
FW	5.1	4.9	4.1	4.0	928	918	1084	1150
JL	4.5	3.6	3.6	3.7	813	1028	1017	964
AA	3.3	3.5	3.2	3.4	1189	1152	1244	1226
AS	3.9	3.2	3.4	3.3	1119	1229	1083	1292
BB	7.0	6.3	6.1	6.1	514	629	588	542
AF	6.3	5.1	5.8	6.4	473	574	490	508
TM	5.5	5.6	5.2	5.1	664	774	667	711
MEAN	4.9	4.3	4.3	4.4	820	950	892	935
SEM	0.42	0.42	0.38	0.41	83	89	87	103

*missing value due to technical problems with equipment.

APPENDIX 3

Individual data from four groups of rats who had cardiac index and portal venous inflow measured after a 20 minute infusion of saline or 1, 2 or 4µg/kg/hr SMS 201-995. Mean arterial blood pressure is shown in mmHg, cardiac index in ml/min/kg and portal venous inflow as % of cardiac output for each rat.

	RAT NUMBER 1	2	3	4	5	6	MEAN	SEM
MEAN ARTERIAL BLOOD PRESSURE								
Controls								
0min	130	110	100	110	100	75	104.2	7.4
20	120	100	105	125	90	75	102.5	7.6
1µg/kg/hr SMS 201-995								
0	120	85	80	105	85	90	94.2	6.2
20	100	60	80	105	90	110	90.8	7.6
2µg/kg/hr SMS 201-995								
0	100	90	85	105	80	100	93.3	4.0
20	75	75	60	100	95	105	85.0	7.2
4µg/kg/hr SMS 201-995								
0	65	100	100	130	70		93.0	11.8
20	80	100	105	130	70		97.0	10.4
CARDIAC INDEX								
Controls	153	214	216	247	240	161	205.1	16.2
1µg/kg/hr	210	225	240	174	287	421	260.6	35.6
2µg/kg/hr	322	176	188	244	354	664	324.8	73.7
4µg/kg/hr	165	140	206	239	318		213.7	31.1
PORTAL VENOUS INFLOW								
Controls	15.3	13.9	13.8	15.3	15.6	13.9	14.6	0.3
1µg/kg/hr	12.8	17.1	16.9	15.6	14.1	8.9	14.2	1.3
2µg/kg/hr	10.9	15.8	15.6	14.6	14.1	5.2	12.7	1.7
4µg/kg/hr	17.7	9.3	13.1	15.7	9.0		13.0	1.0

APPENDIX 4

Individual data for mean arterial and mean portal pressure in two groups of six normal rats given intravenous infusion of saline for 80 minutes or saline followed by doubling doses of 1, 2 and 4 μg/kg/hr SMS 201-995 for 20 minutes at each dose. Mean arterial pressure is shown in mmHg, mean portal pressure is shown in cm water.

	RAT NUMBER 1	2	3	4	5	6	MEAN	SEM
MEAN ARTERIAL PRESSURE								
CONTROL GROUP								
20min	105	119	68	109	91	90	96.9	7.3
40min	91	106	81	106	104	108	99.3	4.4
60min	61	120	100	103	94	102	96.5	7.9
80min	89	96	94	100	95	97	95.1	1.6
SMS 201-995 GROUP								
saline	89	108	119	109	100	81	101.1	5.8
1μg/kg/hr	84	104	108	99	103	74	95.4	5.5
2μg/kg/hr	94	96	126	90	89	64	93.1	8.0
4μg/kg/hr	85	90	133	81	66	53	84.6	11.1
MEAN PORTAL PRESSURE								
CONTROL GROUP								
20min	11.4	8.0	4.2	9.5	4.4	7.1	7.4	1.1
40min	9.6	8.9	4.9	9.3	4.4	7.5	7.4	0.9
60min	12.1	9.1	7.0	9.1	5.6	7.6	8.4	0.9
80min	10.5	7.3	7.8	8.6	4.7	8.0	7.8	0.8
SMS 201-995 GROUP								
saline	8.3	5.7	3.4	9.6	10.4	6.0	4.2	1.1
1μg/kg/hr	8.8	7.3	5.4	9.3	9.7	6.7	7.9	0.7
2μg/kg/hr	9.2	9.1	8.1	8.6	8.8	6.3	8.3	0.4
4μg/kg/hr	8.7	7.5	8.4	8.7	7.5	5.2	7.7	0.5

APPENDIX 5

Individual data for mean arterial and mean portal pressure in three groups of three day post portal vein ligation rats given intravenous infusion of saline for 80 minutes, saline followed by doubling doses of 1, 2 and 4 μg/kg/hr SMS 201-995 for 20 minutes at each dose or saline followed by doubling doses of 8, 16 and 32 μg/kg/hr SMS 201-995 at each dose. Mean arterial pressure is shown in mmHg, mean portal pressure is shown in cm water.

	RAT NUMBER 1	2	3	4	5	6	MEAN	SEM
MEAN ARTERIAL PRESSURE								
CONTROL GROUP								
20min	110	136	105	108	117	106	113.6	4.8
40min	98	135	111	90	97	104	105.7	6.6
60min	100	125	97	93	66	97	96.1	7.7
80min	102	140	75	95	67	105	97.5	10.5
SMS 201-995 GROUP ONE- 1-4 μg/kg/hr								
saline	129	99	95	98	110	90	103.5	5.8
1μg/kg/hr	94	86	105	98	86	90	93.3	3.7
2μg/kg/hr	125	100	87	90	83	79	94.1	6.9
4μg/kg/hr	134	74	66	109	84	65	88.6	11.2
SMS 201-995 GROUP TWO- 8-32 μg/kg/hr								
saline	104	123	125	115			116.6	4.7
8μg/kg/hr	113	142	127	130			128.1	6.0
16μg/kg/hr	113	120	130	122			121.3	3.5
32μg/kg/hr	111	118	130	123			120.5	4.0

(continued overleaf)

APPENDIX 5 continued

	RAT NUMBER 1	2	3	4	5	6	MEAN	SEM
MEAN PORTAL PRESSURE								
CONTROL GROUP								
20min	12.9	15.8	12.3	17.3	11.3	17.5	14.5	1.1
40min	12.0	15.0	7.3	17.4	11.3	17.5	14.6	1.3
60min	11.4	14.1	10.7	16.5	8.4	14.6	12.6	1.2
80min	10.5	12.0	8.1	16.2	8.4	15.0	11.7	1.4
SMS 201-995 GROUP ONE - 1-4 µg/kg/hr								
saline	17.5	16.8	14.8	18.5	15.9	15.4	16.5	0.6
1µg/kg/hr	14.3	14.5	13.0	18.2	12.9	13.3	14.4	1.0
2µg/kg/hr	16.6	11.7	9.8	16.6	13.4	10.1	13.0	1.2
4µg/kg/hr	15.4	7.8	7.6	17.2	12.9	7.9	11.5	1.7
SMS 201-995 GROUP TWO - 8-32 µg/kg/hr								
saline	22.4	22.3	18.5	19.5			20.7	1.0
8µg/kg/hr	22.3	20.4	18.0	17.7			19.6	1.1
16µg/kg/hr	22.4	21.5	20.0	17.7			20.4	1.0
32µg/kg/hr	22.8	24.5	20.3	16.5			21.0	1.7

APPENDIX 6

Individual data for mean portal pressure and %portasystemic shunting in two groups of six three day post portal vein ligation rats given a 30 minute intravenous infusion of either saline or 4μg/kg/hr SMS 201-995. Mean portal pressure is shown in cm water. Portal pressure and %portasystemic shunting measured in each rat before and after the infusion period.

	RAT NUMBER 1	2	3	4	5	6	MEAN	SEM
MEAN PORTAL PRESSURE								
CONTROL GROUP								
Before	19.1	21.1	21.0	16.3	13.7	14.1	17.5	1.4
After	13.8	14.2	18.5	9.7	9.7	12.4	13.0	1.3
SMS 201-995 GROUP								
Before	8.6	10.9	14.6	18.3	14.2	21.1	14.6	1.9
After	4.2	9.4	10.2	14.0	8.1	19.9	11.0	2.2
%PORTASYSTEMIC SHUNTING								
CONTROL GROUP								
Before	50.7	1.0	89.5	57.9	26.4	32.9	43.1	12.4
After	48.2	15.4	94.4	55.9	35.2	8.1	42.9	12.7
SMS 201-995 GROUP								
Before	35.0	5.1	74.3	84.6	76.1	68.7	57.3	12.6
After	15.3	6.1	52.7	87.0	63.0	82.5	51.1	13.8

APPENDIX 7

Individual data for mean portal pressure and %portasystemic shunting in two groups of twenty-eight day post portal vein ligation rats given a 30 minute intravenous infusion of either saline or 4μg/kg/hr SMS 201-995. Mean portal pressure is shown in cm water. Portal pressure and %portasystemic shunting measured in each rat before and after the infusion period.

	RAT NUMBER 1	2	3	4	5	6	MEAN	SEM
MEAN PORTAL PRESSURE								
CONTROL GROUP								
Before	10.1	13.8	9.1	11.4	13.8	9.7	11.3	0.8
After	6.8	11.9	6.8	9.6	14.6	9.0	9.8	1.2
SMS 201-995 GROUP								
Before	10.4	9.9	12.6	10.5	6.3		9.9	1.0
After	11.3	8.8	12.3	10.1	5.8		9.6	1.1
%PORTASYSTEMIC SHUNTING								
CONTROL GROUP								
Before	65.3	61.6	51.2	30.6	43.7	82.4	55.8	7.4
After	74.7	56.3	56.3	25.6	41.7	98.8	58.9	10.4
SMS 201-995 GROUP								
Before	91.0	58.5	6.4	32.4	55.3		48.8	14.2
After	71.0	52.3	10.4	61.8	63.3		51.9	10.7

APPENDIX 8

Individual data for liver function tests, mean portal pressure and %portasystemic shunting in two groups of nine cirrhotic rats given a 20 minute intravenous infusion of either saline or 4μg/kg/hr SMS 201-995. Bilirubin(Bili) is shown in μmol/l, albumin(Alb) in g/l, alanine transaminase(ALT) in units/l, aspartate transaminase(AST) in units/l and alkaline phosphatase(AP) in units/l. Mean portal pressure is shown in cm water. Portal pressure and %portasystemic shunting measured in each rat before and after the infusion period.

	RAT NUMBER 1	2	3	4	5	6	7	8	9	MEAN	SEM
LIVER FUNCTION TESTS											
CONTROL GROUP											
Bili	10	5	6	3	3	3	3	10	2	5	1
Alb	14	9	26	44	25	18	10	25	18	21	3
ALT	29	12	145	125	53	67	63	190	67	83	19
AST	225	285	355	475	225	195	235	395	170	284	34
AP	670	205	425	435	235	300	370	475	260	375	49
SMS 201-995 GROUP											
Bili	5	13	21	7	5	7	8	5	5	8	2
Alb	21	20	15	16	20	16	17	24	22	19	1
ALT	57	420	470	68	40	68	83	93	97	155	55
AST	370	1410	530	190	150	420	250	260	320	433	128
AP	300	380	335	340	225	495	555	280	350	362	35

(continued overleaf)

APPENDIX 8 continued

	RAT NUMBER 1	2	3	4	5	6	7	8	9	MEAN	SEM
MEAN PORTAL PRESSURE											
CONTROL GROUP											
Before	18.5	5.4	13.0	16.4	16.3	10.3	5.4	19.1	8.3	12.5	1.8
After	17.1	6.8	12.4	14.0	14.7	6.9	3.8	18.7	7.9	11.4	1.7
SMS 201-995 GROUP											
Before	14.8	11.8	10.4	9.8	9.5	17.9	14.5	11.8	10.2	12.3	0.9
After	15.6	13.0	9.1	7.7	8.3	17.3	12.0	11.0	11.0	11.6	1.1
%PORTASYSTEMIC SHUNTING											
CONTROL GROUP											
Before	8.7	4.7	14.0	10.7	13.6	44.1	33.0	9.3	29.1	18.6	4.5
After	4.7	2.7	13.3	15.9	9.3	34.3	52.1	38.4	24.1	21.6	5.6
SMS 201-995 GROUP											
Before	11.9	8.2	1.9	5.7	35.5	37.0	8.0	25.1	2.1	15.0	4.6
After	29.9	2.7	2.6	26.7	61.2	29.2	6.7	18.2	7.2	20.5	6.3

APPENDIX 9a

Individual patient data for the 20 variceal bleeds treated with oesophageal tamponade. Characteristics of the patients and the details of the bleed prior to admission to the study. Times are shown in hours.

PT NO	AGE	AETIOLOGY	BLEED NO	ADM CHILD'S	PREADM BLOOD TRANS (mls)	TIME FROM OVERT BLEED	SEVERITY
1	34	alcohol	1	C	1500	38	moderate
4	65	alcohol	4	A	-	1	mild
7	67	pbc	1	C	-	24	mild
8	63	alcohol	1	C	2400	43	mild
10	44	alcohol	2	C	3200	22	severe
11	38	alcohol	1	C	800	72	mild
15	58	alcohol	7	C	-	4	mild
16	61	cah	2	B	1200	29	mild
17	29	alcohol	2	C	-	5	moderate
18	61	cah	3	C	-	3	mild
21	56	cah	6	C	-	8	moderate
23	30	alcohol	3	C	800	30	mild
25	70	crypt	1	C	400	6	mild
26	32	alcohol	3	B	1200	16	severe
30	30	alcohol	1	C	3200	25	severe
32	67	alcohol	3	C	-	2	mild
35	66	crypt	3	C	400	7	mild
36	50	crypt	2	C	-	48	mild
37	64	alcohol	2	B	1000	9	moderate
38	46	alcohol	5	B	-	17	mild

pbc=primary biliary cirrhosis
cah=chronic active hepatitis
crypt=cryptogenic cirrhosis

APPENDIX 9b

Individual patient data for the 20 variceal bleeds treated with oesophageal tamponade. Details of treatment and its results during the study period and outcome of that admission to hospital. Times are shown in hours.

PT NO	INITIAL CONTROL	TIME OF CONTROL	COMPLETE CONTROL	TIME OF REBLEED	X-OVER TIME	BLOOD TRANS (mls)	OUTCOME
1	y	0	y	-	-	1000	alive
4	y	0	y	-	-	800	alive
7	y	1	y	-	-	1800	alive
8	y	0	y	-	-	800	alive
10	y	0	-	-	-	2000	died at 5 hrs
11	y	1	y	-	-	800	died at 9 days
15	y	0	y	-	-	1200	alive
16	y	0	n	33	-	2000	alive
17	y	0	y	-	-	1600	alive
18	y	0	n	16	-	4000	died at 4 days
21	y	1	y	-	-	1200	alive
23	y	0	y	-	-	800	alive
25	y	0	n	47	-	1600	died at 9 days
26	y	2	n	10	-	2400	alive
30	n	-	-	-	2	5600	died at 40 hrs
32	y	0	y	-	-	2000	alive
35	y	0	y	-	-	1600	alive
36	y	0	y	-	-	800	alive
37	y	0	y	-	-	1400	alive
38	y	0	y	-	-	1200	alive

APPENDIX 10a

Individual patient data for the 20 variceal bleeds treated with SMS 201-995 infusion. Characteristics of the patients and the details of the bleed prior to admission to the study. Times are shown in hours.

PT NO	AGE	AETIOLOGY	NO	BLEED CHILD'S	ADM BLOOD TRANS (mls)	PREADM TIME FROM OVERT BLEED	SEVERITY
2	64	alcohol	2	C	-	24	mild
3	68	alcohol	1	C	2800	36	moderate
5	75	alcohol	1	C	-	1	severe
6	28	chf	1	B	1600	24	mild
9	75	alcohol	2	C	-	3	moderate
12	44	alcohol	1	A	-	7	moderate
13	49	alcohol	1	B	3600	71	mild
14	29	alcohol	1	C	-	25	moderate
19	45	alcohol	2	C	-	7	moderate
20	32	alcohol	1	B	800	22	mild
22	74	crypt	2	B	1200	29	mild
24	32	alcohol	2	A	-	7	mild
27	65	drug	5	C	-	3	mild
28	49	pbc	2	C	2000	19	severe
29	46	alcohol	4	B	1200	18	moderate
31	43	sclch	1	B	2000	24	mild
33	50	alcohol	2	C	-	5	mild
34	50	alcohol	1	C	1600	9	moderate
39	33	alcohol	3	B	-	6	mild
40	46	alcohol	6	B	-	18	mild

chf=congenital hepatic fibrosis
pbc=primary biliary cirrhosis
sclch=sclerosing cholangitis
drug=methotrexate induced cirrhosis
crypt=cryptogenic cirrhosis

APPENDIX 10b

Individual patient data for the 20 variceal bleeds treated with SMS 201-995 infusion. Details of treatment and its results during the study period and outcome of that admission to hospital. Times are shown in hours.

PT NO	INITIAL CONTROL	TIME OF CONTROL	COMPLETE CONTROL	TIME OF REBLEED	X-OVER TIME	BLOOD TRANS (mls)	OUTCOME
2	y	0	y	-	-	1600	alive
3	y	1	n	24	24	5600	alive
5	n	-	-	-	4	2000	alive
6	y	0	y	-	-	1200	alive
9	y	1	n	45	-	800	alive
12	n	-	-	-	1	2400	alive
13	y	4	y	-	-	1200	alive
14	y	0	y	-	-	2000	alive
19	y	1	n	9	9	2400	alive
20	y	2	y	-	-	800	alive
22	y	0	y	-	-	800	alive
24	y	0	y	-	-	1200	alive
27	y	0	n	22	22	2200	alive
28	y	2	n	22	-	2400	alive
29	y	1	n	16	-	2000	alive
31	y	0	y	-	-	800	alive
33	y	0	y	-	-	800	alive
34	y	0	n	24	24	2400	alive
39	y	0	y	-	-	800	alive
40	y	0	n	44	-	800	alive

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