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AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCKADE WITH ATRACURIUM.

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This thesis is submitted for the degree of Master of Science in the University of Glasgow.

The work described in this thesis was undertaken in the University Department of Anaesthesia, Western Infirmary, Glasgow.

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CONTENTS

	List of tables.	3
	List of illustrations.	4
	Acknowledgements.	6
	Summary.	8
	Introduction.	11
1.	Pharmacology of atracurium; neuromuscular junction - anatomy and physiology; monitoring of neuromuscular transmission.	12
2.	Relevant aspects of basic control engineering.	45
3.	Feedback control of muscle relaxation - historical background.	55
4.	Equipment.	76
5.	Development of a control system for neuromuscular blockade.	87
6.	Automatic control of neuromuscular blockade with atracurium using a PI algorithm incorporating a preloaded integral.	101
7.	Effect of propofol on atracurium-induced neuromuscular blockade maintained by a feedback system.	109
8.	Automatic control of neuromuscular blockade in patients requiring cardiopulmonary bypass.	119
	Conclusions.	137
	References.	140
	Appendix 1.	154
	Appendix 2.	162

LIST OF TABLES

1. Previous work on automatic control of neuromuscular blockade.
2. Results - P control.
3. PI algorithm with preloaded integral - patient data.
4. PI algorithm with preloaded integral - duration, mean T1, standard deviation and coefficient of variation.
5. PI algorithm with preloaded integral - root mean square deviation, point count and dose.
6. Propofol study - patient details.
7. Mean T1, standard deviation and coefficient of variation before propofol.
8. Mean T1, standard deviation and coefficient of variation after propofol.
9. Root mean square deviation, point count and dose (ug $kg^{-1}min^{-1}$) before propofol.
10. Root mean square deviation, point count and dose (ug $kg^{-1}min^{-1}$) after propofol.
11. Cardiopulmonary bypass study - patient details.
12. Cardiopulmonary bypass study - results.

LIST OF ILLUSTRATIONS

1. Degradation pathway for atracurium (from ref. 10).
2. Schematic diagram of the two-compartment open model: A - standard, B - atracurium (from ref. 33).
3. Schematic representation of the neuromuscular junction (from ref. 41).
4. Schematic diagram of muscle compound action potential with methods of measurement (from ref. 58).
5. Diagramatic representation of feedback control methods: a,c - adaptive; b,d - adaptive (from ref. 68).
6. Datex Relaxograph.
7. Vicker's Treonic IP3 syringe pump.
8. Research Machines Ltd. 380Z-D microcomputer.
9. Circuit diagram - Vicker's Treonic syringe pump.
10. Arrangement of equipment for use in theatre.
11. Process reaction curve (after Ziegler and Nichols). R - slope, L - lag time.
12. Positioning of Relaxograph electrodes.
13. Application of process reaction curve to Relaxograph trace.
14. Relaxograph trace obtained using P control.
15. Relaxograph trace obtained using PI control.
16. Relaxograph traces obtained using PI control with preloaded integral: A - with initial overshoot above 20%; B - without overshoot.
17. Histogram showing doses of atracurium in steady state period using PI control with preloaded integral.
18. Effect of propofol on steady level of neuromuscular blockade. Propofol bolus at mark 3.

19. Effect of propofol on steady level of neuromuscular blockade. Propofol bolus at mark 4.

20. Automatic control of neuromuscular blockade with atracurium in a patient undergoing coronary artery vein grafting (see text).

21. Automatic control of neuromuscular blockade with atracurium in a patient undergoing coronary artery surgery (see text).

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SUMMARY

The objective of this work was to develop a robust feedback system to control atracurium-induced neuromuscular blockade. The controller ideally should be usable in many circumstances and should provide a steady background blockade to allow investigation of drug interactions and physiological changes. A particular design constraint was that the system should not cause any delays in the running of a normal theatre list.

Several groups have studied the automatic control of neuromuscular blockade with other relaxants. Atracurium seemed to be a suitable drug to use because of its relatively short duration of action, its non-cumulative properties and its relatively narrow dosage range.

In the development of the control system four step tests were undertaken from which proportional and integral gains were derived. Then, trial runs with proportional (P) and proportional-integral (PI) controllers were evaluated and the solution to the problems discovered with these methods was to preload the integral.

A series of 36 patients was analysed whose neuromuscular blockade was maintained by the PI controller with preloaded integral. The results from these patients showed that a steady level of neuromuscular blockade, which was close to a predetermined target of 20% baseline T1, could be obtained with this system. In no case did the level of blockade oscillate, indicating that the control system was robust - the doses required to maintain constant blockade ranged from 2.7 ug $kg^{-1}min^{-1}$ to 8.6 ug $kg^{-1}min^{-1}$ with a mean of 5.4 ug $kg^{-1}min^{-1}$. Use of

the system did not lead to any significant delays in the running of lists. Blockade control was sufficiently precise and accurate to provide a background for the analysis of the effects of potential physiological and pharmacological perturbations to the system. Such studies should provide further information on the pharmacology of atracurium.

This work describes the largest series of patients to have undergone automatic control of neuromuscular blockade with atracurium. The quality of the blockade in our work was superior to previous work both in terms of stability and closeness to target.

Previous work on the possible potentiation of atracurium by propofol has produced conflicting results. In our work, long cases involving minimal physiological upset were selected to provide a stable blockade for the analysis of the effect of a bolus of propofol on the system. It was concluded that propofol had no clinically significant effect on atracurium.

The final group of patients investigated were undergoing coronary artery vein grafting. Automatic control systems for neuromuscular blockade have not previously been used in cardiac surgery. Cardiac patients were selected for a number of reasons. Firstly, the start of cardiopulmonary bypass (with its associated hypothermia and haemodilution) would provide a challenging test to the robustness of the system. Could this, for example, induce sustained oscillation in the control system? Secondly, we wished to see the specific effects of haemodilution and hypothermia on the level of block. If steady blockade

could be achieved at different stages of the operation the atracurium requirement could be compared.

The controller was able to provide satisfactory relaxation in all cases. It was generally possible to separate the effects of haemodilution and hypothermia. We concluded that haemodilution attenuated, while hypothermia potentiated, neuromuscular blockade induced by atracurium. It was possible to show that the atracurium requirement was unchanged in the postbypass stage compared with the prebypass stage. This conclusion differed from previous studies in which a force transducer was used rather than the electromyogram.

In summary, a feedback control system for atracurium has been developed, tested and used to investigate the effect of propofol on atracurium and the effects of cardiopulmonary bypass on a steady state neuromuscular blockade.

INTRODUCTION

The work of this thesis draws on material from the disciplines of medicine and engineering. An outline of the relevant important aspects of each of these fields is provided in the first three chapters.

Chapter one describes the pharmacology of atracurium, the physiology and anatomy of the neuromuscular junction, and methods of monitoring neuromuscular function.

This is followed by an account of the basic principles of control engineering as they relate to medicine in general and to neuromuscular blockade in particular. The importance of the Ziegler-Nichols rules in the design of adaptive and non-adaptive control systems is emphasised.

In the third chapter a summary of the work carried out to date on the automatic control of neuromuscular blockade by other workers is given with special reference to the types of control system used and the results obtained.

These three chapters, therefore, lay the foundations for the clinical research described in the succeeding chapters. The objectives of the research are described in the summary.

CHAPTER 1

PHARMACOLOGY OF ATRACURIUM

Atracurium besylate was developed by Professor JB Stenlake of Strathclyde University (1). It is one of the most recent attempts to develop an ideal muscle relaxant, the desired properties of which have been described by Jones (2):

1. Rapid onset of action
2. Relatively short duration of action
3. Prompt and reliable reversal
4. Cardiovascular stability
5. No cumulation
6. Metabolic products pharmacologically inactive
7. No histamine release
8. Safe in presence of compromised liver or kidney function

DEVELOPMENT

The competitive neuromuscular blocking agents used before the introduction of atracurium suffer from a number of drawbacks. The most important of these are lack of complete specificity for the neuromuscular junction (leading to cardiovascular side-effects) and prolonged paralysis (in patients with kidney or liver disease, genetically-determined enzyme deficiencies or old age).

The key to the unique properties of atracurium lies in the elimination pathway described by AW Hofmann in 1851. This pathway depends on the chemical degradation of

quaternary ammonium salts and normally requires treatment with strong alkali at 100°C:

$$HO^- + H\text{-}CH_2\text{-}CH_2\text{-}N^+R_3 \longrightarrow H_2O + CH_2{=}CH_2 + NR_3$$

The reaction is promoted by electron withdrawal because of the positive charge on the quaternary nitrogen and therefore can be induced to occur at lower pH and temperature by the presence of electron-attracting substituents on the B-carbon.

Stenlake set out to synthesise a bis-quaternary compound which had structural features giving a competitive and selective neuromuscular blocking action and which was capable of undergoing biodegradation to inactive quaternary compounds. It was necessary to strike a balance between rapid degradation at physiological pH in vivo and satisfactory stability at lower pH (3.5) and temperature (4°C) to allow preparation and storage. Several compounds were synthesised and finally atracurium (coded as BW33A) solubilised as a besylate salt was selected.

Atracurium is also degraded by ester hydrolysis which does not require pseudocholinesterase and is facilitated by an acid pH. Breakdown of atracurium both by Hofmann elimination and by ester hydrolysis is shown in fig. 1. Metabolism of atracurium is the subject of much current work and will be discussed in more detail later.

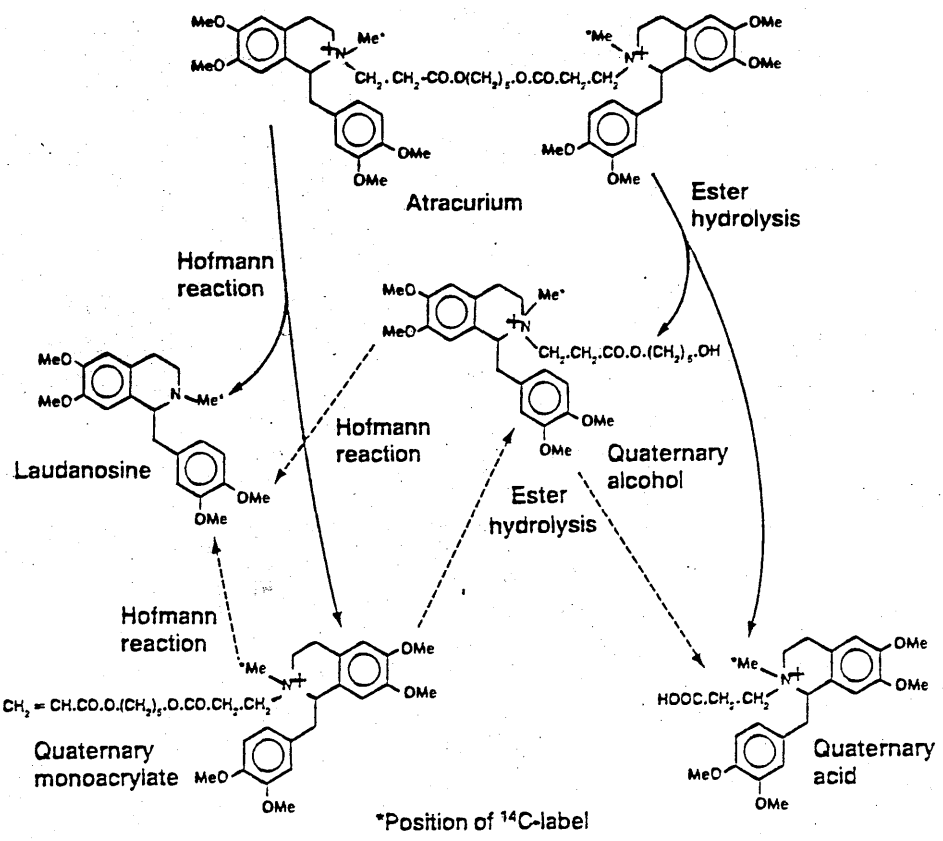


Figure 1. Degradation pathway for atracurium (from ref. 10)

DOSAGE, POTENCY, ONSET, RECOVERY and REVERSAL

The manufacturers recommend the following doses. For adults and children over one year, 0.3-0.6 mg kg^{-1} as an initial bolus provides satisfactory blockade for 15-35 minutes. This can be supplemented by boluses of 0.1-0.2 mg kg^{-1} as required. For intravenous infusion doses of 0.005-0.01 mg $kg^{-1}min^{-1}$ are suggested.

A drug which is more potent than a comparable drug will produce the same effect at a lower dose. Potency can be considered in terms of intensity or duration of effect. In terms of intensity, effective dose 95 (ED95) is taken as the standard for comparison - ED95 is the dose required to produce 95% depression of twitch height. Using this criterion vecuronium is 5.0 times as potent as atracurium and pancuronium 4.3 times as potent (3).

Suxamethonium is still the most rapidly acting of the neuromuscular blockers and in situations where speed of onset is of utmost importance it remains the drug of choice. Satisfactory intubating conditions are obtained with 0.6 mg kg^{-1} atracurium in 90 seconds. Reliably good intubating conditions cannot be achieved in less than 60 seconds regardless of the dose used (4).

The duration of action of a single dose of atracurium is dependent on the size of the dose. Defining recovery time as the time to 90% spontaneous twitch recovery, Basta et al (5) found the following recovery times: 0.2 mg kg^{-1} - 44minutes; 0.4 mg kg^{-1} - 63 minutes; 0.6 mg kg^{-1} - 76 minutes. 0.2 mg kg^{-1} corresponds to an ED95 dose.

Atracurium shows a very clear tendency towards spontaneous recovery without the need for specific

antidotes. Once the recovery phase has begun the rate of recovery is independent of the dose of atracurium (6). An important property of atracurium is that the rate of recovery from neuromuscular blockade is significantly faster than with traditional agents. This is thought to reflect different degrees of pre and postsynaptic effects.

The overall consequence of the above observations is that on many occasions specific reversal of the neuromuscular blocking effects of atracurium will not be required. This has a number of advantages. Firstly, avoidance of atropine may prevent tachycardia and the development of a state which could be mistaken for blood loss. Secondly, relative overdose of neostigmine is capable of causing an acetylcholine-induced block which may last for up to 20 minutes. Thirdly, the administration of neostigmine may be associated with an increased incidence of disruption of bowel anastomoses following abdominal surgery (7).

The rate of recovery from atracurium can be enhanced by the use of anticholinesterase agents such as neostigmine and edrophonium (8).

HISTAMINE RELEASE

Normal plasma histamine concentration lies between 0.3-1.0 ng ml^{-1} (9). Concentrations of 2-5 ng ml^{-1} are associated with increased heart rate, flushing and hypotension. These may be a result of true anaphylactic reactions or anaphylactoid reactions. The important factor is the ratio of the dose of drug causing histamine release to that producing satisfactory clinical effects.

Atracurium is associated with histamine release and produces a high incidence of essentially cutaneous manifestations, most of which are harmless allergoid reactions resulting from skin histamine release. Systemic anaphylactoid reactions also occur.

The most serious problem relating to histamine release with atracurium is so-called "aggregate anaphylaxis". This occurs when saline flushings between drugs are not used allowing the formation of mixed, precipitated drugs. The resulting precipitate (particularly thiopentone/atracurium) is capable of causing acute life-threatening bronchospasm.

The incidence of adverse reactions involving atracurium reported to the Committee on Safety of Medicines (CSM) between December, 1982 (the date of introduction of the drug into clinical practice in the UK) and February, 1985 (during which time approximately 1 000 000 patients received the drug) was low. Bronchospasm occurred in one in 63 000, anaphylactoid reactions in one in 143 000 and cardiac arrest in one in 250 000 (10).

CARDIOVASCULAR EFFECTS

Muscle relaxant effects on the cardiovascular system are due to histamine release, antagonism of acetylcholine at sites other than the neuromuscular junction or sympathetic stimulation (2). Generally, these effects are unwanted.

It is necessary to draw a distinction between cardiovascular effects in healthy patients and those with pre-existing cardiac disease. Barnes et al (11) studied

fit, young adults. They found that the change in heart rate following a bolus of 0.6 mg kg^{-1} was minimal and that, although there was a transient decrease in arterial pressure in 28% of patients, by four minutes after injection the change in blood pressure was minimal. Moyers et al (12) studied patients with severe cardiovascular disease and concluded that atracurium was effective and safe although rapid administration of large doses (0.5-0.6 mg kg^{-1}) might cause transient hypotension. They suggested that significant haemodynamic effects could be minimised by using small boluses at thirty second intervals.

It has been reported that atracurium may cause bradycardia during fentanyl anaesthesia (13). This may be explained on the basis of vagal surgical stimulation in the presence of a narcotic agent known to slow heart rate.

DRUG INTERACTIONS

Anaesthetic agents enhance competitive neuromuscular blockade in the following order: nitrous oxide-narcotics < halothane < isoflurane and enflurane (14). Atracurium and vecuronium appear to be less influenced by the choice of anaesthetic than curare or pancuronium. The augmentation of atracurium-induced blockade by enflurane and isoflurane is only 20-30% greater than the augmentation produced by halothane or nitrous oxide-narcotic anaesthesia. The figures for pancuronium and tubocurarine are about 100% (15).

There is some disagreement in the literature regarding the possible potentiation of atracurium by

diisopropyl phenol. Robertson et al (16) found that diisopropyl phenol potentiated the effect of atracurium but not its duration of action. Nightingale et al (17) concluded that "no statistically significant differences were found for any of the measurements of neuromuscular blockade with ..... non-depolarising neuromuscular relaxants". In Robertson's study diisopropyl phenol was solubilised in Cremophor while in Nightingale's work diisopropyl phenol was in an emulsion. The picture is further complicated by the observation that Cremophor alone will antagonise vecuronium and pancuronium (18). The effect of propofol on atracurium is discussed in a later chapter.

There is also some evidence to suggest that suxamethonium administration before atracurium may increase the intensity of block but has little or no effect on the duration of block.

METABOLISM AND EXCRETION

Atracurium undergoes degradation at physiological temperature and pH by a self-destroying mechanism (Hofmann elimination) to give laudanosine and a quaternary monoacrylate as metabolites. Laudanosine may then undergo enzymic N-demethylation to tetrahydropapaverine. Atracurium also undergoes ester hydrolysis to form a quaternary alcohol and a quaternary acid (fig. 1).

Work continues on the role of organ metabolism in the breakdown of atracurium. Ward and Neill (19) concluded that "the elimination half-life of atracurium is unaffected by both renal and hepatic failure" and Fahey et al (20) stated that there was no difference in the

pharmacokinetics and pharmacodynamics of atracurium in patients with normal renal function and those with renal failure. Both these papers emphasise the pre-eminence of Hofmann elimination in the breakdown of atracurium. More recent work questions this premise. Fisher et al (21) concluded that hepatic or other non-renal pathways accounted for 61% of the clearance of atracurium and that Hofmann elimination and ester hydrolysis accounted for the remaining 39%. They did not comment on the relative contributions of the two latter processes but said that elimination of atracurium seemed to depend little on renal function. The full story is probably not yet known but there is no doubt that, whatever the contributions of the different mechanisms to the elimination of atracurium, the drug behaves clinically as though its metabolism is not organ-dependent, certainly in the case of patients with compromised renal function.

Much has been written about laudanosine. The effects of this substance are very interesting but probably largely irrelevant (this view is shared by Professor JP Payne) (22). The interest in laudanosine has been generated by the knowledge that this substance will produce convulsions in animals. This was first reported by the French workers Mercier and Mercier in 1955 in a paper referred to by Ingram et al (23). Standaert (24), acknowledged that "laudanosine is a modest stimulant of the central nervous system that may sometimes cause seizures". Shi and colleagues (25) found that laudanosine increased anaesthetic requirement in the rabbit while

Lanier et al (26) concluded that laudanosine produced from atracurium caused CNS stimulation in dogs.

Standaert (24), commenting on these two papers, stated that anaesthetists should be prepared to increase the amount of inhaled anaesthetic especially if a prolonged infusion of atracurium was used but felt that the risk of convulsions was negligible.

Large doses of atracurium administered to anaesthetised dogs led to clonic seizure activity when the plasma concentration exceeded 17 ug ml^{-1} (27). In man levels no higher than 5.1 ug ml^{-1} have been recorded in intensive care patients with renal failure maintained at full neuromuscular blockade for several days (28).

A potential problem exists in patients with severe hepatic disease. The elimination half-life of laudanosine is prolonged and it must be anticipated that relatively high concentrations may develop following prolonged infusion in patients with hepatic failure (29).

EFFECT OF AGE

D'Hollander et al (30) showed that, in contrast to the other competitive neuromuscular blockers, reduced doses of atracurium were not required to sustain a steady state of paralysis in the elderly patient. Also recovery from neuromuscular blockade was not prolonged.

Goudsouzian et al (31) concluded that both the dose required for intubation and the duration of action of atracurium was not significantly different in children over two years of age from adults.

PHARMACOKINETICS

Pharmacokinetics is the quantitative study and mathematical analysis of drug and drug metabolite levels in the body. The topic is reviewed by Hull (32).

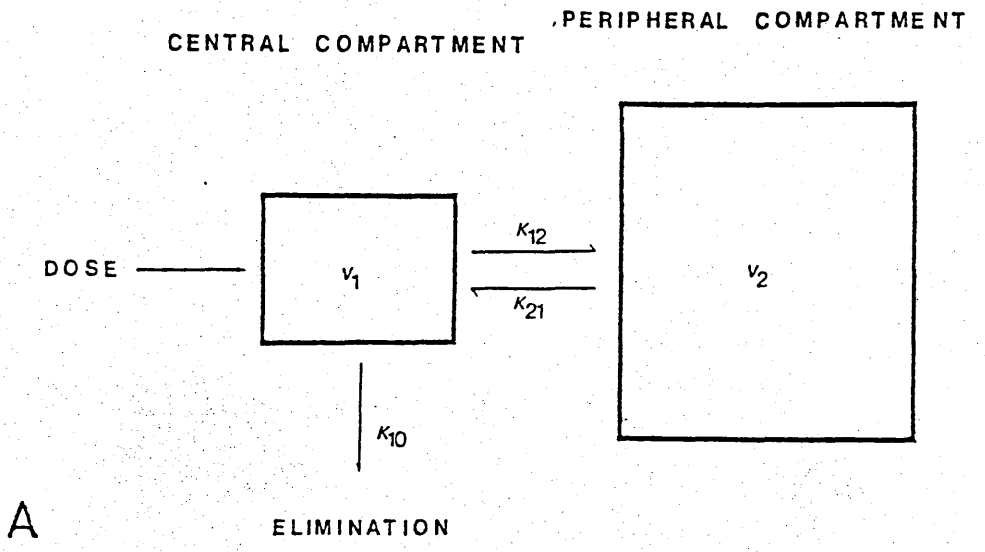
Many drugs used in anaesthesia follow a plasma concentration versus time profile which is consistent with a two compartment open pharmacokinetic model. In such cases a log plasma concentration versus time graph shows a bi-exponential decline pattern. A two compartment model consists of a relatively small central compartment, into which the drug is administered and from which it is eliminated, and a peripheral compartment throughout which the drug is distributed (fig. 2A).

The initial rapid fall in concentration (alpha phase) is largely due to drug redistribution from the central to the peripheral compartment and the subsequent slower fall (beta phase) is largely due to elimination from the central compartment. There is inevitably some overlap between the two processes. Both redistribution and elimination are first-order processes, i.e. the rate at which they occur is proportional to the amount of drug in the relevant compartment.

Generally, in clinical practice drugs are best given at intervals approximately equal to their half-lives (half-life - $T_{1/2}$ - the time taken for the plasma concentration to fall by 50%). When this rule is followed there tends to be a progressive rise in plasma concentration for four to five half-lives until steady state concentrations are reached.

Theoretically, in a single-compartment model (the drug is administered to and eliminated from one compartment without being redistributed to another compartment), the desired concentration can be arrived at immediately by giving a loading dose which is the product of desired plasma concentration and volume of the central compartment (V_1). The problem with a two-compartment model is that of selecting which is the appropriate volume. If V_1 is chosen, the appropriate concentration will be rapidly reached but will not be maintained because of redistribution; if the apparent volume of distribution (V_B - the volume in which the drug is contained following redistribution) is chosen, then the initial plasma concentration will be much too high but will fall to the desired value. Once the appropriate concentration has been attained it can be maintained by an infusion, the rate of which is the product of desired concentration and plasma clearance. Unfortunately, both volumes of distribution and clearance are subject to considerable inter-individual variation.

The kinetics of atracurium do not follow this classical pattern. Ward et al (33) propose a modified two compartment model. In this modified model an additional rate constant is included to allow for elimination from the peripheral compartment (fig. 2B). Hull (34) agrees with Ward's reasoning but feels that the standard two-compartment model is still suitable. Ward's group give



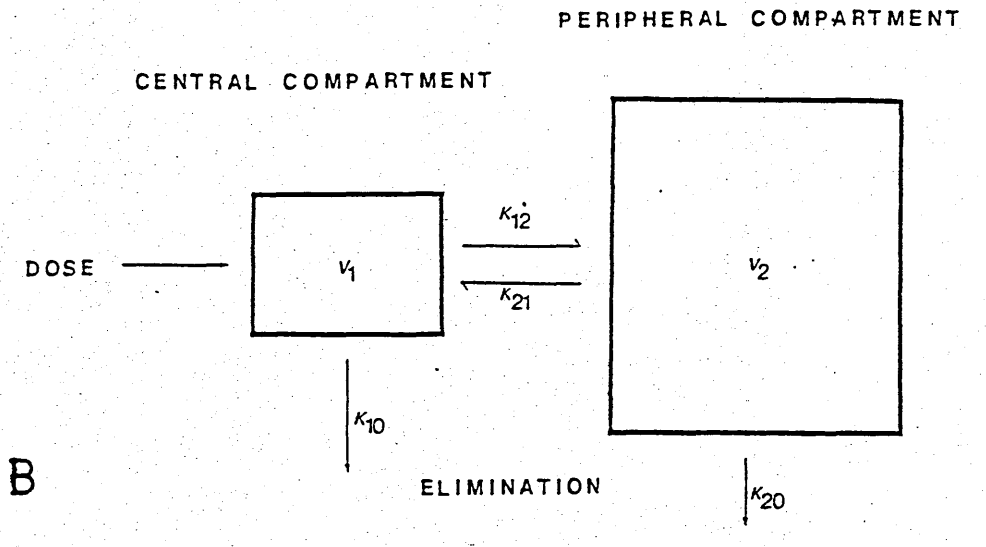


Figure 2. Schematic diagram of the two-compartment open model.

A. Standard B. Atracurium

(from ref. 33)

the following values for the various pharmacokinetic parameters for atracurium:

1. $T_{1/2}$ alpha - 2.00 minutes
2. $T_{1/2}$ beta - 20.0 minutes
3. V_1 - 49 ml kg^{-1}
4. V_B - 157 ml kg^{-1}
5. Clearance - 5.5 ml $min^{-1}kg^{-1}$

These values indicate that atracurium has a relatively short elimination half-life and a small volume of distribution. These features indicate it to be suitable for intravenous infusion.

PHARMACOKINETICS OF ATRACURIUM INFUSION

As indicated above, the elimination rate and volume of distribution can be calculated from kinetic studies of bolus injections into the central compartment. For an infusion the entry rate is known. When the infusion is stopped, the elimination function is demonstrated alone, as with a bolus except that the effect of any deep compartment will be more apparent since this compartment will be approaching equilibrium with the plasma compartment.

One of the basic facts of infusion kinetics is that plasma concentration and physiological effect are maintained at a desired level more efficiently in terms of drug administered, and therefore more safely, by an infusion rather than by repeat bolus doses (35).

Using the kinetic and dynamic parameters provided by Weatherley, Williams and Neill (36), Williams (35) has calculated the profile of neuromuscular blockade for a regimen comprising a loading dose of 0.6 mg kg^{-1} followed

by an infusion of 0.0066 mg $kg^{-1}min^{-1}$, which maintained a 95% blockade. He also calculated the minimum repeat bolus doses required at 15 and 30 minute intervals to maintain the blockade at 95% or greater. Large overdose troughs occurred with the repeat bolus methods and the total drug dose required was greater.

One is forced to the inevitable conclusion, consequently, that for long-term relaxation, intravenous infusion is the method of choice.

In many branches of surgery deep and relatively constant levels of muscle paralysis are required to facilitate the surgeon's work. This is particularly true of abdominal surgery.

Until recently, the standard method of administration of neuromuscular blockers was to give a weight-dependent loading dose followed by repeat bolus injections of one-third to one-fifth of the loading dose (37,6). These repeat injections are given according to clinical signs or impressions of the anaesthetist or surgeon or merely on a "by-the-clock" basis. While usually clinically satisfactory, this method produces badly controlled levels of neuromuscular blockade and overdosage of relaxant at the end of the operation is likely. This problem can be overcome to some extent by titrating doses on the basis of the results of effective monitoring and there is a growing body of anaesthetic opinion which feels that routine monitoring of neuromuscular blockade is mandatory in the paralysed patient.

Appropriate rules for the dosage of atracurium have been laid down by d'Hollander et al (38).

In summary, atracurium is a non-depolarising muscle relaxant which has a relatively short duration of action and minimal side-effects. The exact mechanism of its metabolism is still not clear but it behaves as if it is not dependent on organ function for its elimination. It has a relatively short half-life and a small volume of distribution - these properties indicate that it is a suitable drug for infusion.

NEUROMUSCULAR JUNCTION - ANATOMY AND PHYSIOLOGY

It is a fundamental rule of pharmacology that learning about drugs must be based on a sound knowledge of physiology. A work of this kind must therefore contain an account of the basic physiology of neuromuscular transmission.

ANATOMY

The synapse between the motor nerve and the muscle is the neuromuscular junction. The nerve splits into numerous small fibres as it approaches the muscle. Muscles associated with relatively gross movements (such as the postural muscles of the back) are innervated in such a way that each nerve supplies a relatively large number of muscle fibres; muscles associated with fine movements (such as those of the hand) are innervated so that each nerve supplies only a small number of fibres.

A motor nerve and the muscle fibres it supplies is known as a "motor unit" and each motor unit responds in an "all-or-none" manner, i.e. on stimulation of the nerve each muscle fibre contracts maximally or not at all.

All motor nerves pierce the muscle epimysium at about midway between the origin and insertion - the "motor point". The motor nerve then breaks up into neurofibrils which innervate the muscle. Having reached the motor point, each neurofibril loses its myelin sheath and comes to lie in a groove on the muscle fibre. It remains separated from the muscle by the synaptic cleft. The synaptic cleft is separated from the extracellular fluid by the Schwann cell membrane (39) and is deeply furrowed

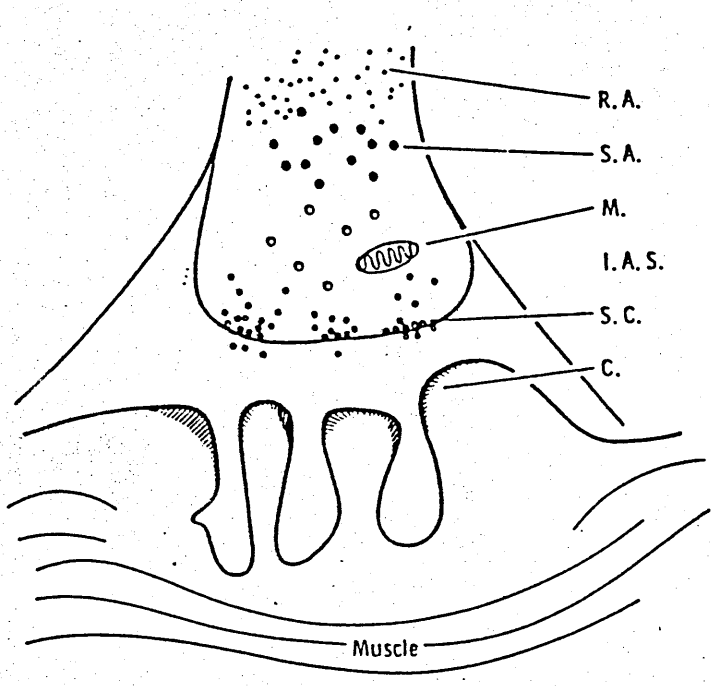
by secondary clefts (fig. 3). Around the openings of these secondary clefts are the receptors for acetylcholine. This region is also rich in cholinesterase (40). Acetylcholine is released from discrete areas on the motor nerve terminal directly opposite these secondary clefts.

PHYSIOLOGY

Acetylcholine formation and release

Acetylcholine is formed by the acetylation of choline within the nerve by a complex system of enzymes including acetyl CoA and acetyl transferase. The choline is transported into the nerve by an active carrier system from the extracellular fluid. Once in the nerve cell, acetylcholine is packaged into vesicles pending its release from the nerve terminal. Each vesicle contains 4-5x10^5 molecules of acetylcholine. These vesicles discharge their contents at random to cause a miniature end-plate potential (MEPP) at the motor end-plate. Each MEPP causes a depolarisation at the motor end-plate of 1-2 mv - this is the sort of voltage that would be expected from opening about 1500 sodium pores on the post-synaptic membrane. In order to cause a propagated action potential at least 20 to 30 times as many sodium pores must be opened. The formation and release of acetylcholine is now recognised to be a quite complex procedure. Acetylcholine is thought to exist in the nerve ending in three separate states:- storage, reserve and immediately available (41). Only the immediately available acetylcholine can be released immediately following motor nerve stimulation.

Normally, acetylcholine is rapidly hydrolysed by cholinesterase at the postsynaptic membrane. The choline



R.A. = reserve acetylcholine
S.A. = storage acetylcholine
M. = mitochondria
I.A.S. = immediately available source of acetylcholine
S.C. = synaptic cleft
C. = cholinesterase around mouth of 2° cleft

Figure 3. Schematic representation of the neuromuscular junction (from ref. 41)

released from this process is then available for re-uptake by the motor nerve and resynthesis to acetylcholine. Some of the acetylcholine diffuses away from the receptor site to be hydrolysed in the bloodstream.

Neuromuscular Transmission

At rest there is a potential difference of about 90 mv (outside positive relative to inside) across the post-synaptic membrane which is the resting membrane potential (RMP). This voltage is the result of a surplus of positively charged ions outside the membrane relative to inside and is generated as follows. At rest the membrane is much more permeable to potassium ions than it is to sodium ions. As the concentration of potassium ions is much higher inside the cell than outside, potassium continually diffuses down this concentration gradient and out of the cell. This efflux of positively charged ions generates an electrical gradient which is opposite in direction to the concentration gradient. When the two gradients are of equal magnitude the RMP is arrived at. The RMP is, therefore, essentially a potassium diffusion potential. According to the Gibbs-Donnan law:

$$\text{emf} \propto [K^+] \text{ inside cell}/[K^+] \text{ outside cell}$$

Consequently, a decrease in extracellular potassium concentration will increase the RMP making it more difficult for acetylcholine to depolarise the membrane and therefore potentiating non-depolarising muscle relaxants.

When acetylcholine reacts with the postsynaptic cholinoreceptors it opens the sodium channels for a brief period (about 1-1.5 milliseconds) and allows the entry of

some 12,000 cations. This causes the transmembrane potential to change from -ve 90 mv to zero or +ve 10 mv. This change in potential is usually sufficient to cause a propagated action potential to pass along the muscle resulting in contraction.

Towards the end of depolarisation potassium conductance increases as sodium conductance falls to its original level. The excess of intracellular sodium is expelled gradually by the sodium pump mechanism.

In common with most other physiological processes in nature, the neuromuscular junction possesses a large margin of safety. At least 70% of the function of the neuromuscular junction has to be lost before neuromuscular failure begins to occur and at least 80% of the activity has to be blocked by neuromuscular blockers before the twitch response is affected (42).

The foregoing is a simplified outline of the process occurring at the neuromuscular junction (41). Much research has taken place in recent years into the exact mechanism of neuromuscular transmission and two fields have attracted special interest - the role of calcium and the function of prejunctional cholinoreceptors.

Calcium

An action potential along the motor nerve is the stimulus for the release of neurotransmitter at the nerve ending. Calcium is an essential intermediary before this can occur. Depolarisation or sodium influx alone will not produce release of transmitter but the addition of calcium (e.g. by microinjection into the nerve ending) will cause transmitter release even in the absence of

depolarisation (43). The number of quanta released depends not only on the calcium concentration in the extracellular fluid but also the length of time during which calcium flows into the nerve ending. These two factors indicate that the crucial factor is therefore the total number of calcium ions in the nerve cell ending after stimulation. The calcium current begins about the time the action potential reaches its maximum depolarisation and persists until the membrane is returned to its normal potential by efflux of potassium ions. It is of interest that agents which slow or prevent potassium efflux (i.e. potassium channel blockers, e.g. 4-aminopyridine, 3,4-diaminopyridine) greatly prolong the duration of calcium influx and consequently the outpouring of neurotransmitter from the nerve ending (as a result 4-aminopyridine antagonises non-depolarising neuromuscular block) (44).

Depolarisation opens channels in the nerve cell membrane that allow calcium to pass into the cell. Cyclic adenosine monophosphate (cAMP) is thought to be the link between membrane depolarisation and the opening of the calcium channel - depolarisation activates membrane-bound adenyl cyclase which converts adenine triphosphate (ATP) to cAMP which acts as a protein kinase causing opening of the calcium channel (2).

Calcium requires the presence of the binding protein calmodulin in order to cause transmitter release. Its existence was first reported independently in 1970 from the USA and Japan. It is a single chain protein of 148 amino acids and has a molecular weight of 16,700. It is folded into four matching groupings each of which has a

binding site for calcium. Attachment of calcium to each binding site alters the configuration of the calmodulin molecule and activates it. This complex then activates a receptor protein. It is thought that calmodulin is required for several stages of the process leading from depolarisation to transmitter release. The exact mechanism by which calcium causes release of neurotransmitter is not yet known. The presence of the ion in the active zone appears to start a process which leads to the vesicle membrane fusing with the cell membrane and therefore forming a direct route from the centre of the vesicle to the synaptic cleft. The transmitter leaves the the vesicle and diffuses across the junctional cleft to react with receptors on the motor end-plate or be destroyed by cholinesterase or both.

The role of prejunctional receptors

There is undeniable evidence for the presence of acetylcholine receptors on the presynaptic area of the motor nerve. There is, however, no broad agreement on the exact role of these receptors.

They have been invoked as a possible explanation for the phenomena of tetanic fade and train-of-four (ToF) fade in the presence of partial non-depolarising neuromuscular block. The classical explanation is that acetylcholine output per nerve impulse, even in the absence of partial block, decreases rapidly during high frequency stimulation. This is not normally reflected in decreasing response because of the considerable margin of safety, both in terms of the number of acetylcholine molecules

released and the excess of cholinoreceptors on the motor end-plate. When the margin of safety is reduced (by partial competitive block) the waning transmitter output is unmasked and becomes manifest as a fading tension response. In other words, the competitive blocker unmasks the effect of decreasing transmitter output but does not per se cause the decrease.

This view is now known to be untenable (45). Normal nerve endings are, in fact, capable of mobilising transmitter very well; there is little or no decrease in the quantal content of rapidly evoked end-plate potentials until curare is introduced, at which point mobilisation is substantially reduced (46).

Bowman (47) feels that this failure of mobilisation must result from an action of the relaxant on the nerve ending. He also comments that the cholinoreceptors which mediate inhibition of mobilisation have a different pharmacological profile from those on the motor end-plate. Essentially the presynaptic receptors are responsible for fade and the postsynaptic receptors for twitch tension depression. Bowman feels that the most likely mode of action is as follows. Transmitter acetylcholine acts on prejunctional receptors to mobilise transmitter from the reserve to the immediately available store. Blockade of these prejunctional receptors impairs mobilisation and so causes fade. If one further supposes that the pre and postsynaptic receptors are of slightly different structure then the different selectivity of different antagonists in terms of the degree of fade caused relative to the twitch depression can be explained.

MONITORING OF NEUROMUSCULAR TRANSMISSION

In the past, the level of neuromuscular blockade has been assessed on purely clinical grounds (muscle tone, the occurrence of spontaneous muscular movements, the "feel" of the anaesthetic reservoir bag, the ability to open the eyes, to cough and to sustain a head-lift) (2). In recent years there has been a trend towards more accurate monitoring of neuromuscular function and this has been accelerated by the advent of the newer muscle relaxants, atracurium and vecuronium.

Why is monitoring of neuromuscular transmission thought to be important? Viby-Mogensen (48) argues that there are three main reasons: the great variation in individual sensitivity to myoneural-blocking drugs; the margin of safety (i.e. the number of receptors on the motor end-plate far exceeds the number required to trigger a muscle action potential under normal conditions); the relationship between the degree of non-depolarising block and the effect of an anticholinesterase drug. He maintains that routine use of a nerve stimulator allows precise individual dosage of relaxants and their antagonists.

At the beginning of an operation, monitoring of neuromuscular blockade is useful in order to indicate the time at which intubation can be reliably accomplished. There are a number of conflicting factors to be taken into account. First, there are certain circumstances in which traumatic, cough-free intubation is deemed essential, e.g. certain types of ophthalmic surgery and neurosurgery; second, some anaesthetists feel that rapid intubation is

important, e.g. during busy operating lists; third, on occasion it is necessary to intubate the patient with as small a dose of relaxant as possible, e.g. in day-case anaesthesia (49) or in our work on automatic control (where it is important that neuromuscular function recovers to a residual EMG level of 20% of baseline as rapidly as possible so that the automatic controller can be switched in). Clearly these different aims are incompatible.

Post-operatively, monitoring of neuromuscular transmission may be important in order to assess the adequacy of reversal of neuromuscular block, e.g. in a patient with compromised respiratory function.

Intra-operatively, there are two reasons for monitoring the degree of block - first, to determine the optimal time for incremental doses and second, to assess the potential or necessity for reversal.

PRINCIPLES OF NERVE STIMULATION

Electrical stimulation of a motor nerve in a non-paralysed patient will produce contraction of those muscles supplied by the nerve. The reaction of a single muscle fibre to a stimulus follows an all-or-none law - there is maximal contraction of the muscle fibre if the stimulus intensity exceeds a certain threshold. If the motor nerve is stimulated with sufficient intensity to recruit all the muscle fibres in the motor unit, then the stimulus is said to be supramaximal.

The administration of a muscle relaxant will cause the force of contraction to be reduced. Measuring the

reduction in contraction force at unchanged supramaximal stimulation indicates the degree of neuromuscular block.

There are traditionally three types of neuromuscular blockade. These were described initially by Churchill-Davidson and co-workers (50, 51).

1. Non-depolarising block - induced by competitive neuromuscular blocking drugs and characterised by the absence of fasciculation before onset of block; presence of fade and post-tetanic potentiation; antagonism by anticholinesterases; potentiation by other non-depolarisers and antagonism by depolarisers.
2. Depolarising block - induced by agents such as suxamethonium and characterised by muscle fasciculation preceding the onset of the block; absence of fade and post-tetanic potentiation; potentiation of the block by anticholinesterases and antagonism by non-depolarisers.
3. Phase II block - said to occur when a block which initially has the features of a depolarising block takes on the characteristics of a non-depolarising block. This occurs with prolonged infusion or repeated use of suxamethonium.

As noted above, until recently monitoring of neuromuscular blockade was carried out on clinical grounds. Respiratory variables can also be monitored -

respiratory frequency, tidal volume, vital capacity, inspiratory force and peak expiratory flow rate were examined by Ali et al (52). These relatively crude methods are fraught with problems, however. Assessment of voluntary movement requires an awake, co-operative patient; depression of respiratory variables may occur as a result of a relative overdose of opiates or inhalational agents.

The only reliable method of monitoring neuromuscular function is to stimulate an accessible peripheral nerve and to measure the evoked response from the innervated muscle (53).

METHODS OF MEASUREMENT OF EVOKED RESPONSE

The responses of skeletal muscle to direct stimulation can be measured visually, by touch, electrically or mechanically. The following comments refer to stimulation of the ulnar nerve at the wrist.

1. Visual - the arm is abducted to 90^{o} in supination. With single stimuli thumb movement is evaluated and compared with baseline; with ToF stimulation the object is to count the number of visible responses and if four twitches are present to attempt to quantify the ToF ratio (in general the presence of four twitches signifies a T1 of greater than 25%). In practice the response to a tetanic stimulus is more relevant. No fade in a tetanic stimulus of five seconds

duration correlates with a ToF ratio of at least 0.7 and therefore clinically acceptable recovery.

2. Tactile - it is easier to detect the presence of any twitch tactilely than visually and also easier to count the number of twitches. It remains difficult to assess the ToF ratio accurately and once again tetanic stimulation is advised to indicate adequate reversal.

Mechanical and electromyographic monitoring require discussion in more detail.

Mechanical measurement usually employs the small muscles of the hand and usually the thumb. The adductor pollicis brevis is the only muscle supplied by the ulnar nerve involved in thumb adduction and as such approaches the precision of Merton's experimental nerve-muscle preparation (54). Stimulating electrodes are applied either as surface or percutaneous needle electrodes along the ulnar nerve at the wrist or elbow and the tension developed by the muscle is recorded. In order for the results to be correct and reproducible the contractions must be isometric - consequently, a preload must be applied and maintained. In effect the thumb acts as a force-displacement transducer and the force of contraction is converted into an electrical signal and then amplified. The important points concerning mechanical measurements are that transducer placement is correct, that a preload is used and maintained and finally that the transducer is not overloaded. Ali and Savarese (55) in a review of the

monitoring of neuromuscular function discuss transducer overload in some detail. The maximum force of adduction of the thumb in normal volunteers is about 8 kg and this figure exceeds the capacity of some force transducers. If this is the case then a true control tension cannot be recorded. As a result during recovery from neuromuscular block the tetanic response may appear well-sustained when in reality there is still a significant degree of block present.

Evoked electromyography (EMG) is more versatile than evoked tension (56). The EMG can be measured from the adductor pollicis brevis, the abductor digiti quinti or the first dorsal interosseous muscle of the hand in response to ulnar nerve stimulation. The active electrode is placed over the motor point of the muscle to be studied and the indifferent electrode at the tendon of insertion of that muscle. An earth electrode should be placed between the stimulating and recording electrodes. Using the EMG avoids the problems, outlined above, with transducer fixation, orientation and overload which are potential sources of error with evoked tension measurement. If the recording electrodes are correctly placed over the motor point, a number of biphasic motor unit action potentials are recorded as a single compound action potential. The stimulus artefact detected before the action potential represents the arrival of the electrical impulse at the recording electrodes. The stimulus artefact can be diminished by gating the response, i.e. recording the response for a set time period in an attempt to exclude the stimulus artefact. The

Datex Relaxograph (57) records the response from 3-10 milliseconds after the nerve stimulation.

At this point the signal requires to undergo further processing and this can take one of two forms (58, fig. 4). The amplitude of the compound action potential signal can be measured or the signal can be rectified and the area under the curve integrated (59). The potentials picked up are quite small in amplitude and require amplification to a degree that can be conveniently studied.

A number of instruments are now available to enable measurement of these high-speed events. These can process the raw EMG signal in response to ToF stimuli which are generated by a built-in stimulator. The computer searches automatically for the supramaximal stimulus and establishes the baseline response. The Datex Relaxograph, which is one of these instruments, also computes the ratio of the height of the first response in the train to the height of the control response and the ratio of the fourth response to the first.

PATTERNS OF NERVE STIMULATION

Currently four patterns of motor nerve stimulation are in use.

A. Single Twitch Stimulation

Epstein and Epstein have defined proper stimulus characteristics (60). The stimulus should be a square wave pulse to avoid repetitive firing and a tetanus-like response. The duration should be as short as possible, around 0.2 ms. If the duration of the stimulus is greater

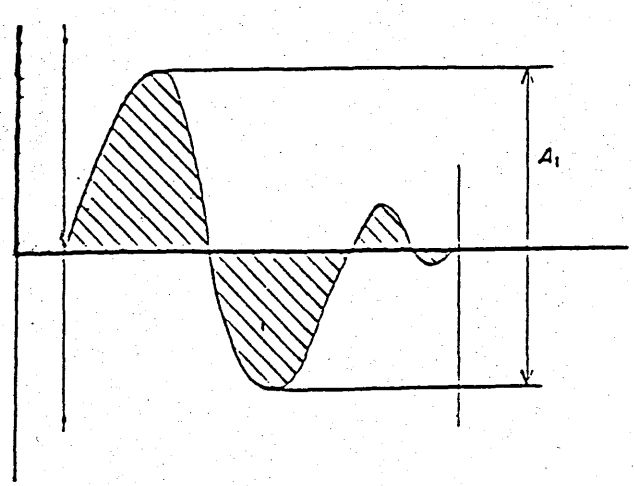


Figure 4. Schematic diagram of muscle compound action potential with methods of measurement.

Shaded area = area for integration

A_1 = peak height

(from ref. 58)

than the refractory period of the nerve, a second action potential will be generated by the falling phase of the stimulating pulse. In addition, excessively long pulses may stimulate the muscle directly. The stimulus intensity should be supramaximal to ensure activation of all fibres. The stimulus frequency is also important. Changing it significantly alters the effective dose of competitive relaxant required to achieve a certain point on the dose-response curve. Ali and Savarese (61) reported that if the frequency of the single twitch is changed from 0.1 to 1.0 Hz the ED95 for curare will decrease by a factor of three or more. Also the onset time and duration of action differ. They concluded that the ED95 of curare at 0.1 Hz was more clinically relevant because this corresponded with degrees of relaxation adequate for smooth tracheal intubation and satisfactory surgical relaxation.

Single twitch stimulation is suitable for studies comparing different neuromuscular blockers. After obtaining a baseline response, the percentage change from baseline establishes the onset time and potency of the drug. The duration of action is indicated by the time required for recovery of the response to baseline level. The recovery index is given by the time for recovery from 25% to 75% of baseline to occur. The limitations of the single twitch are as follows: baseline heights must be obtained before the administration of muscle relaxants and complete stability of recording over a period of time is not certain. Post-operatively single twitch is useful in differentiating central and peripheral causes of apnoea.

B. Tetanic stimulation

As noted earlier, tetanic fade is a prejunctional phenomenon arising from the effect of curare-like drugs on mobilisation of acetylcholine during high-frequency stimulation. In situations where the margin of safety is reduced (myasthenia gravis or competitive neuromuscular blockade), a decrease in acetylcholine output will result in a non-sustained contraction or fade of the evoked muscle response to tetanic contraction.

There are a number of problems associated with monitoring neuromuscular blockade by tetanic stimulation (2). It induces recovery in the muscles stimulated so that all subsequent events are shifted toward normality and it is painful to perform in the conscious patient. Jones (2), however, argues that, in the absence of sophisticated monitoring equipment, the most convenient and accurate way of ensuring that a patient has achieved a safe degree of recovery from neuromuscular blockade is by application of a sustained tetanus of 50 Hz for five seconds. An absence of fade detected either visually or tactilely to this stimulus indicates a T4 ratio of 0.7 or greater.

C. Post-tetanic single twitch stimulation

This term refers to repeated single twitches applied six to ten seconds after cessation of tetanic stimulation. Post-tetanic potentiation during partial curarisation can be explained on the basis of increased mobilisation and synthesis of acetylcholine during and after tetanic stimulation. Post-tetanic potentiation can be used for the

assessment of profound degrees of neuromuscular block when there is no response to single-twitch, ToF, or tetanic stimulation. Viby-Mogensen et al (62) demonstrated that during pancuronium-induced blockade, the response to post-tetanic twitch stimulation occurred 36 minutes before the first response to single-twitch stimulation. They further showed that the degree of block could be quantified by counting the number of single twitch responses elicitable after the tetanic stimulus.

D. Train-of-four stimulation

One of the main advantages of ToF stimulation is the facility it gives to assess the degree of neuromuscular blockade without the necessity for a control value in the unparalysed state. Four supramaximal stimuli are administered at a frequency of 2 Hz, not more often than once every 10 seconds. Ali et al (63) concluded that the ratio of the fourth to the first evoked response provided a convenient method of assessing neuromuscular transmission. It does not require a baseline measurement and causes much less discomfort to the patient than tetanic stimulation. Another important point is that it does not affect the amplitude of any subsequent response, in contrast to tetanic stimulation.

During the onset of neuromuscular blockade, the fourth response in the train is eliminated at approximately 75% depression of T1; the third response is abolished at 80% diminution of T1; the second at 90% (56).

RELATIONSHIP BETWEEN EVOKED RESPONSE AND CLINICAL BLOCK

There is considerable confusion even among anaesthetists regarding the relationship between the finite values of results obtaired from evoked responses and the degree of clinical neuromuscular blockade associated with these finite values. The relationship is, however, relatively clearly defined.

With a T4 ratio of 60% or above, patients were able to sustain head-lift for at least three seconds (64). Ali and co-workers (52) found that in conscious, unmedicated volunteers, the changes in tidal volume, vital capacity, inspiratory force and peak expiratory flow rate at a T4 ratio of 60% were negligible compared to baseline. A T4 ratio of 70% correlates with the return of the single twitch at 0.15 Hz to baseline height and a sustained mechanical response to tetanic stimulation at 50 Hz for five seconds (65).

The range of 95% to 75% neuromuscular block is generally agreed to define clinically acceptable relaxation (55).

This section has attempted to indicate the different methods of assessing neuromuscular function, to describe the different patterns of stimulation which can be used to provide information about the neuromuscular junction and finally to indicate how the various parameters so derived relate to the clinical state of the patient in terms of relaxation, potential for reversal and recovery.

CHAPTER 2

RELEVANT ASPECTS OF BASIC CONTROL ENGINEERING

This chapter gives a brief outline of the relevant principles of control engineering. Further details can be found in the work of Yousefzadeh (66) and Brown (67). Control engineering is becoming increasingly important in medicine, both in the analysis of biological systems and in patient management.

DEFINITIONS

There is no consistent terminology in the control literature. I have adopted that used by Vozeh and Steimer (68). Their paper describes the concept of feedback control methods for drug dosage optimisation from the point view of control theory.

A control system is an arrangement of physical components connected in such a manner as to continuously command, direct or regulate itself or another system.

From the point of view of drug therapy the control system is divided into five parts (fig. 5).

1. The patient is the central part of the control system and, in the present project, his neuromuscular blockade is the controlled process. This is described by a mathematical model that defines the relationship between dose and response. This is a complex function involving parameters that may change depending on clinical conditions and patient characteristics.
2. The dosage represents the input to the controlled process. Generally, the more

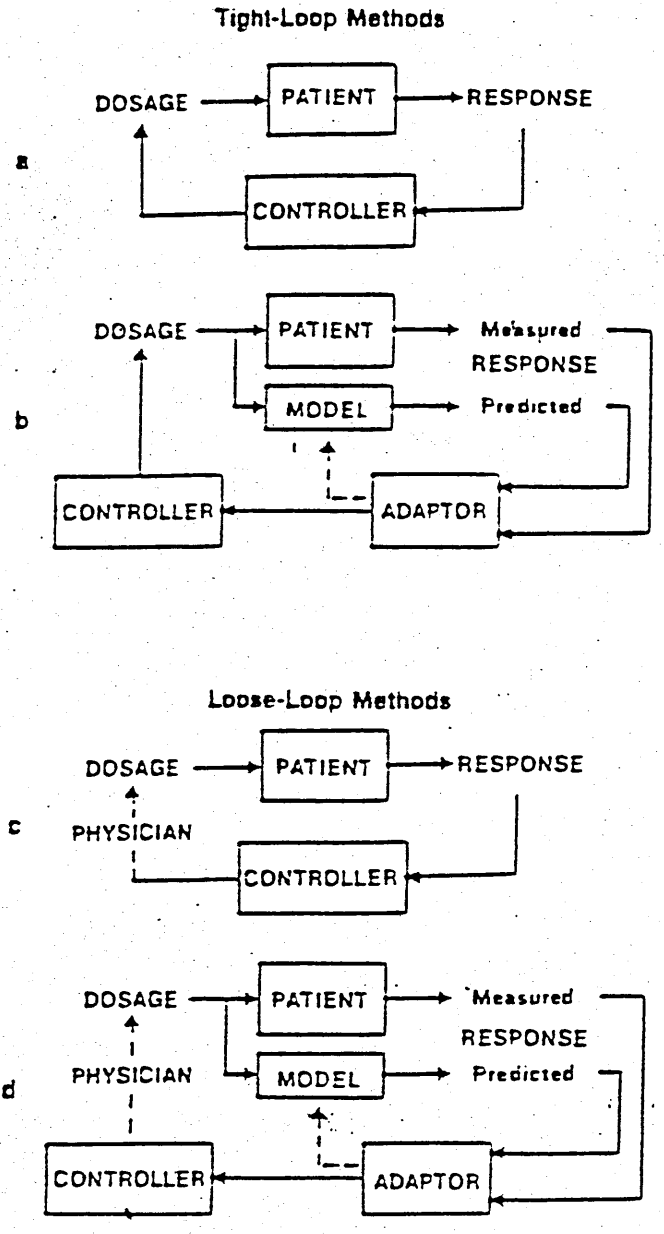


Figure 5. Diagramatic representation of feedback control methods

a, c non-adaptive

b, d adaptive

(from ref. 68)

complicated the dosage scheme the more prone it is to human and computer error.

3. The response is the output of the process - the feedback information that is being measured. Ideally, the true therapeutic endpoint (e.g. how "tight" the abdomen is during general surgical procedures) should be used but in practice an intermediate endpoint (e.g. the magnitude of the T1 of the compound EMG) which has a high predictive value for the true endpoint may have to be used.
4. The adaptive element is used to update the parameters of the model which describes the relationship between the dose and response according to the most recent measurement. Not all control systems contain an adaptor.
5. The controller determines the dosage strategy based on the observed response.

It is worth commenting on some other terms at this juncture. Classic control theory defines the input differently from above. It is the reference variable or the required value for the output. This is subsequently referred to as the target (or set-point).

Error - the difference between the output and the target. This is the value which is applied to the control mechanism and is used to drive the controlled variable in the appropriate direction.

In a closed loop control (CLC) system the input chosen for control at a particular time is a function of the output. In open loop control, the input is not related

to the output. All systems subsequently described are closed-loop. Vozeh and Steimer further classify control systems into two main groups - loose-loop control occurs when the doctor's interaction is included in the control loop and tight-loop when it is not. All methods subsequently described are tight-loop (fig. 5).

FEEDBACK CONTROL

The feedback principle is the basis of operation of CLC systems, which are required to work accurately and in a stable fashion over long periods. The object is to cause the output to follow the target.

Feedback control systems can be divided into two categories: regulator systems and follow-up systems. A regulator system is designed to keep the controlled variable constant (by this yard-stick, the control system described in this thesis is a regulator system). A follow-up system is a feedback control system whose prime function is to keep the controlled variable in close correspondence with a reference variable which has a frequently or continuously changing value.

A regulator system works as follows. The feedback pathway incorporates a transducer which measures the output and converts it to a form suitable for comparison with the target. The comparator, which is part of the control mechanism, subtracts the feedback signal from the set-point to form the error. The error is then amplified and processed before being applied to the controlled process in such a way as to drive the error toward zero. The purpose of the amplifier is to magnify the error, i.e. a small input to the amplifier produces a large output.

Because the comparator subtracts the feedback signal from the target the system is known as a NEGATIVE FEEDBACK SYSTEM. The behaviour of many biological systems can be analysed and explained in similar fashion, although most biological systems are considerably more complex containing multiple control loops.

Figure 5 illustrates the types of control system in "block diagram" format showing the way in which the different elements are linked together. It is important to know how the output of any component responds when a particular signal is applied at the input to that component. This is where the concept of GAIN comes in. Gain is the ratio of the output of a component to its input. Each component in the system has a gain and the system as a whole has a gain which is the product of the gains of the individual components (the total system gain or loop gain). Instability in a system is likely to result if there is a high loop gain and excessive time lags. If a particular component in the system has a high gain then the output from that component will be large relative to the input. Any component with a particularly high gain is likely to lead to instability in the system by producing a high total system gain. This becomes manifest as follows. A high gain may cause the system to overcorrect for any error, thereby inducing a worse error, further overcorrection and so on. In this way an oscillation builds up and and the system is said to be unstable.

The person in charge of the design of the system must carefully choose the appropriate gain - too low a gain

will result in a system with a sluggish response; too high a gain will lead to the risks of overload and instability.

TYPES OF CONTROL SYSTEM

Control systems can be divided into two broad categories: adaptive and non-adaptive.

Non-adaptive systems

In non-adaptive systems the process is considered as deterministic and known, i.e. it is assumed that the process can be described by a model with constant parameters. Because the parameters remain unchanged, the model need not be explicitly defined and becomes part of the control equation.

In non-adaptive systems the controlling parameters of the system are derived before the system is used and cannot be changed once the system is in use. Hence, it is important that the values of these parameters are determined accurately initially. In practice, a preliminary study on a sample of typical patients is required to learn the features of the dynamic process in the group of interest (see Step Tests later). Significant deviations of the parameters for a given individual from the fixed average values implemented by the model can therefore lead to poor control.

The simplest of the non-adaptive systems is the so-called "bang-bang" system. This operates on the principle that the input to the controlled process is either on or off, e.g. a control system for neuromuscular blockade in which the infusion is either on at a constant rate or off, depending on the response. Although relatively crude, in

certain circumstances the control produced by these systems may be perfectly satisfactory.

More sophisticated controllers have been in existence for a considerable time. These were first succintly described by Ziegler and Nichols in 1942 (69) in one of the classic control engineering works. They described the principal effects found in controllers and provided formulae for determining the controller settings. The three effects were designated "proportional", "automatic reset" and "pre-act". These are now better known as proportional, integral and derivative (P, I, D). A brief description of each is given and then an indication is made of how they interact by means of a relatively simple equation which is relevant to the infusion of muscle relaxants.

1. Proportional Response.

Almost all controllers incorporate proportional response - this means that the output of the controller varies with the error. The "sensitivity" (or gain) of proportional response is a measure of the magnitude of the controller output relative to the error.

Sensitivity affects primarily the stability of control - for any control system there is a point called the "ultimate sensitivity". Above this value the response of any system will oscillate in an increasing fashion to some maximum; below this value the oscillations will decrease to straight line control. The "amplitude ratio" is the amplitude of any wave in an oscillating response to the wave which preceded it and at the "ultimate sensitivity" the amplitude ratio is one.

From the point of view of stability (i.e. minimal oscillation - the lower the gain the less likelihood of instability) a low sensitivity should be chosen but this is bought at a cost. The lower the sensitivity the greater the offset (i.e. at steady state, the difference between the value obtained for the controlled variable and that desired) and the longer the period of oscillation. In general, the best compromise is to pick the sensitivity which gives an amplitude ratio of 0.25. It is found that this sensitivity is about half the ultimate.

2. Integral Action (Automatic Reset)

This is the second most common response found in automatic controllers. Its purpose is to eliminate offset. It detects any disparity between the actual value of the response and the set-point and causes the response to move in the proper direction to correct the error. In the case of the proportional term only the most recent reading is used in the calculation of the output of the controller. In contrast the integral contains the cumulative error - it incorporates the sum of all the previous errors. The disadvantageous features of automatic reset are its tendency to increase the period of oscillation and to promote instability.

3. Derivative Action (Pre-act Response)

This effect simply gives an additional movement of the response proportional to the rate at which the response is occurring. Derivative action helps to stabilise a potentially unstable system and speeds the response of a slow system.

The calculated infusion rate for a PID system would be:

$$\text{Flow} = K_p \times e + K_i \times \int e + K_d \times (e - e')$$

where K_p, K_i and K_d are values for proportional, integral and derivative gains, respectively; and e, $\int e$ and $e - e'$ represent the current error, the cumulated error and the value of the current error minus the previous error, respectively.

Ziegler and Nichols describe methods for deriving the values for these gains.

It is possible to have P only systems, PI systems, PD systems and PID systems (70). The control algorithm employed for the bulk of this thesis uses a PI system.

Adaptive and Self-tuning Control

These methods recognise that some features of the process are unknown and could be estimated as part of the control in order to provide optimum input. There are two problems in relation to drug therapy: to overcome interindividual variability (drug sensitivity) in the input, which is achieved by estimation of individual model parameters (self-tuning control); and to accomodate intraindividual variability through online dosage adjustment if changes in dose requirement are detected (adaptive control).

In general, adaptive systems monitor the parameters of the controlled process and constantly keep the control system "tuned" so that the overall system performance does not degrade over time (in effect altering values for K_p, K_i and K_d) (71). The system's performance is monitored

in some fashion and the control parameters modified accordingly. Also, when adaptive systems are used the control system does not have to be accurately tuned initially - in time it will accurately tune itself.

These types of systems should theoretically be able to cope more efficiently with patients who are particularly sensitive or resistant to the effects of the controlled drug than non-adaptive systems. Further, they should be better able to deal with intra-individual variation (e.g. the effects of sudden rapid blood loss).

The major difference, therefore, between adaptive and non-adaptive systems is that with the adaptive systems modelling can take place while the system is in use (on-line) but with the non-adaptive systems, modelling is complete before the system is used. Adaptive systems are, therefore, more complex from the engineering point of view. Non-adaptive systems are likely to be more robust and still find important uses today.

This chapter has outlined the basic concepts of control engineering with particular reference to the control algorithm employed in the studies described in this thesis. The method of applying these principles to atracurium infusion will be described in subsequent sections.

CHAPTER 3

FEEDBACK CONTROL OF MUSCLE RELAXATION - HISTORICAL BACKGROUND

Several groups have looked at the development of systems for the automatic control of neuromuscular blockade over the last 15 years or so. This chapter is subdivided into sections which look in turn at the contributions from each centre. The work is summarised in table 1.

1. MELBOURNE GROUP

The earliest work was done by an Australian group led by Cass (an anaesthetist) and Lampard (an electrical engineer). Their first paper appeared in 1973 and described a system which carried out computer control of ventilation and the "depth of anaesthesia", as well as neuromuscular blockade. This paper was accompanied by an outline of the principles of control engineering (67).

Lampard, Coles and Brown (72) studied healthy sheep. They used a pulse generator to deliver supramaximal stimuli via a co-axial needle electrode to a peripheral motor nerve. The resulting electromyographic activity was detected by electrodes placed in the body of the contracting muscle. The small potentials produced were amplified, rectified and gated to produce a steady potential whose magnitude reflected the electrical activity in the muscle. A digital computer was used to process the incoming information and provide an

Table 1. Previous work on automatic control of neuromuscular blockade.

CENTRE	RELAXANT	CONTROL ALGORITHM
Melbourne	d-tubocurarine, gallamine, alcuronium, pancuronium, atracurium	bang-bang/adaptive, PI
Sheffield	pancuronium	proportional
Cape Town	d-tubocurarine, atracurium	adaptive
Birmingham	suxamethonium, vecuronium	PID, PI
Amsterdam	vecuronium	bang-bang
London	atracurium	PD

appropriate output of relaxant to maintain a steady level of neuromuscular blockade.

Few details are given concerning the nature of the control mechanism. It is described as being of the "bang-bang" type but also including an adaptive element which is not clearly specified. The syringe was activated in the following way. A constant concentration of relaxant was used and the syringe driver was arranged so that muscle relaxant was injected at a constant rate. Injection occurred for a varying proportion of each minute and the duration of this portion was dependent on the processed error between the integrated EMG and the set point.

The authors concluded that although the control system for neuromuscular blockade was rather sluggish in responding to a change in set-point, it produced a degree of stability which was greater than that which could be achieved by manual control. They felt that it provided ideal conditions for investigation of one variable while others were held constant. Both gallamine and d-tubocurarine were used successfully in these experiments and the results showed a good degree of control.

The second contribution from this team compared four muscle relaxants, again in the sheep. Cass, Lampard, Brown and Coles (73) studied d-tubocurarine, gallamine, alcuronium and pancuronium and expanded upon the methods described in their previous paper.

Two muscles were analysed: the rectus abdominis and the masseter. These were selected because the motor nerves and muscle bodies were accessible, the nerves could be stimulated several centimetres remote from the muscle

(thus eliminating the stimulus artefact) and the rectus abdominis was thought to relate more closely to the requirements of clinical surgery than the usually studied muscles of the forearm and hand. The computer was programmed to sample rectus integrated EMG every two seconds and actuate a motor-driven syringe to inject the appropriate muscle relaxant.

The adaptive element mentioned in the previous paper was clarified to some extent. Every four minutes the anticipated duration of switch-on was updated by analysis of the mean on-time for the previous four minutes. The authors maintained that by this method the expected diminishing requirement of the drug was taken into account.

Relaxants were diluted to what was thought to be an equipotent concentration in that equal volumes of the different relaxants would produce an equivalent suppression of the integrated EMG. The relaxant was given initially in a bolus dose which was calculated to bring the integrated EMG to 40% of control. Recovery was allowed to occur until well advanced and then the controller switched on. As expected the syringe pump was continually on initially until the integrated EMG was relatively close to the set-point. The duration of injection per minute was then continually updated to maintain a constant level of paralysis. During the controlled period the level of control was described as good, although no statistical analysis was given.

Although the results reported by this team indicate good (but not perfect) control of neuromuscular block,

there are a number of practical criticisms of their work. Accurate control of neuromuscular blockade is a laudable aim in its own right but in order to be workable in the clinical setting with human patients a different strategy is needed.

Depending on the type of surgery a profound block may be necessary early in the operation. It is not feasible to allow recovery to almost control levels to occur early in the anaesthetic.

Secondly, strict control of physiological variables during the period of surgery is not possible - interference with physiological variables is an integral part of operative surgery.

Thirdly, 40% of baseline is probably not a sufficiently profound level of blockade to select from the point of view of guaranteeing immobility during surgery.

What the study does demonstrate is the feasibility of obtaining a steady level of blockade (in sheep) and the potential of this as a background for assessing the effect of various physiological or pharmacological interventions.

A further publication by this team reported the effect of hypothermia on the dose requirement of d-tubocurarine in 16 anaesthetised cats. Lam, Brown and Lampard (74) used a modified computer program to maintain a constant level of block incorporating a proportional-integral (PI) system. Unfortunately, no further details of the mechanism of the control system were given.

The interaction between the kinetics and dynamics of muscle relaxants and temperature is complex, with a number of different factors involved. These include the

physiological effects of temperature as well as the pharmacological, e.g. the mechanism of nerve conduction and muscle relaxation. It is consequently difficult to categorically describe a cause and effect relationship.

The workers concluded that much less relaxant was required to maintain a given level of block in the presence of hypothermia (30°C compared with 37°C). They also noted that fine control of the EMG was harder to obtain because of increased fluctuations in drug consumption at lower temperatures.

Cass, Brown, Ng and Lampard (75) described a further study in which a target of 20% integrated EMG was used. Four different relaxants were studied in a single sheep. Each experiment lasted for 110 minutes and was divided into three phases - loading, onset and maintenance. During the loading phase, relaxant was infused at a constant rate until the integrated EMG began to fall, at which point the infusion came under computer control and the integrated EMG was gradually reduced to 20% over a period of 20 minutes. From this point, a level of 20% was maintained by the computer-controlled infusion. The loading phase is that required to "mop up" the margin of safety. The onset phase appeared to demonstrate that the dose-response curves for the different relaxants have different slopes. During the maintenance phase an almost constant dose of relaxant was required to maintain a steady degree of paralysis - this indicated that the elimination of the drug was balanced by the infusion.

The same group produced a companion paper (76) in which the effect of a dose of 0.08 ug kg^{-1} neostigmine,

with atropine, was used to antagonise the effects of d-tubocurarine, gallamine, alcuronium or pancuronium following control of block to 20% baseline EMG for 30 or 90 minutes in a single sheep. Twenty-eight experiments were carried out altogether (three with each drug at 30 minutes and four at 90 minutes). In all cases recovery had occurred within two minutes and the workers concluded that the four relaxants used were equally effectively antagonised by neostigmine. Again no details of the exact control mechanism were given.

The most recent publication by this team (77) described the control of muscle paralysis using atracurium in the sheep. The technique of computer control is described as being the same as that used in the earlier paper comparing four relaxants (73). The main conclusion drawn from this paper was that no progressive decrease in infusion rate was required to maintain a steady level of paralysis (confirming the non-cumulative nature of atracurium - this is true but analysis of the previous results from this group indicate that none of the other four relaxants studied were cumulative using the same criteria (73)).

2. SHEFFIELD GROUP

The second group to undertake a study of automatic control of neuromuscular blockade again involved anaesthetic and engineering co-operation. Two features of this work make it more relevant and interesting than the work of Lampard and co-workers. Firstly it was carried out in human beings and secondly the details are published in engineering as well as anaesthetic journals thus giving

more information on the automatic control mechanism. The first contribution from this team appeared in the setting of a presentation to the Anaesthetic Research Society (ARS).

Asbury, Brown and Linkens (78) described a system of feedback control of neuromuscular blockade using pancuronium in 10 patients undergoing upper abdominal surgery. The ulnar nerve was stimulated at the wrist with single supramaximal stimuli at 10 second intervals. The evoked EMG produced by these stimuli was recorded by surface electrodes placed over the small muscles of the hand. The signal was then filtered, integrated, rectified and stored as a d.c. voltage. This voltage was compared with a reference voltage which represented the desired level of blockade and the difference between the two voltages was used to calculate an appropriate infusion rate to return the level of paralysis to the set target.

Brown and co-workers (79) described a simple proportional controller. The integrated amplitude of the EMG response obtained from stimulation of the ulnar nerve was used as the controlled variable. Baseline recordings were obtained and then the patient given 20 ug kg^{-1} pancuronium as a loading dose and the controller set to attain a target level of 20% of baseline (80% paralysis). Ten patients were studied and a mean level of paralysis of 74.1% with a standard deviation of 4.3 was obtained.

This team encountered a number of problems. They had initially used a mechanical recording of the electrical stimulus but found that this system was subject to movement artefacts and had a higher signal-to-noise ratio

than the EMG. The EMG recording had the disadvantage that it was subject to interference from surgical diathermy - this problem was overcome by manually inhibiting the sample-and-hold measuring system when diathermy was in use. The use of a bolus dose was considered necessary to produce an acceptable level of paralysis relatively early - the workers felt that increasing the gain of the system to a degree where it would obtain satisfactory paralysis by the same time would almost certainly lead to instability. The potential problem with the bolus dose was that if it were too large it would lead to initial total paralysis of the patient and delay the advent of automatic control until a considerable period had elapsed, i.e. until some recovery had occurred.

They concluded that stable control of the level of paralysis could be achieved using closed-loop control of drug infusion and, somewhat tentatively, that the total dose of drug used was less.

In 1981 Asbury et al (80) studied the possibility of an interaction between diazepam and pancuronium in six healthy patients undergoing general surgery. Induction was with methohexitone, intubation facilitated by suxamethonium and anaesthesia maintained using nitrous oxide, fentanyl and droperidol. The same control mechanism as already described was used to maintain 80% paralysis. Once a steady level of paralysis had been achieved, a bolus of 0.14 mg kg^{-1} diazepam was given intravenously over one minute, producing therapeutic blood concentrations. No consistent differences were produced in level of block, blood pancuronium concentration or

pancuronium consumption following the diazepam bolus. As expected, with use of proportional control, the target level was not exactly achieved, the level of paralysis ranging from 71.4% to 72.9% but the standard deviations and coefficients of variation were small indicating that the control system maintained a steady level of paralysis. In one of the six patients there was a significant change in the mean level of block following the diazepam bolus but this was a decrease rather than an increase. Asbury concluded that there is no evidence that diazepam interacts with pancuronium.

This is a very elegant study and its importance lies not so much in the demonstration of a possible interaction between diazepam and pancuronium but in the concept employed. When a stable level of neuromuscular block has been attained it is possible to perturb the system in some way in order to see whether there is a change in the level of blockade or a change in the consumption of neuromuscular blocker. The perturbation need not be of a pharmacologiocal nature - fluid shifts or temperature changes can be studied. The study can be criticised on the grounds that the target level of blockade was not attained and that consequently each patient was running at a slightly different level of paralysis. Also, because of the nature of the control system, the level of paralysis was not exactly consistent and a very transient effect of diazepam could have been overlooked.

This group's most recent contribution was a continuation of the work presented to the ARS in 1980. Forty patients were studied (81) and the results obtained

were similar to the earlier work. Again a proportional controller was used and again there was an offset from the target level. Asbury conceded that this offset could be eliminated with the addition of an integral term. The main problems encountered in this study related to the possibility of introducing delays into the smooth running of theatre lists. He concluded that feedback control of neuromuscular blockade is clinically feasible and that the advent of the new muscle relaxants might allow even more precise control of the level of muscle paralysis.

3. CAPE TOWN GROUP

The next group to examine computer-controlled muscle relaxation was based in Cape Town, again a combination of anaesthetists and engineers. Their early work described the development of a system based on available pharmacokinetic and pharmacodynamic data and subsequent publications tested these algorithms in patients using d-tubocurarine and atracurium. This work is interesting because it was the first attempt to develop a self-tuning program in human beings.

Bradlow et al (82) described a modelling process whereby they produced an input/output relationship between drug dosage and effect for d-tubocurarine. The aim of this was to determine whether d-tubocurarine was best suited to a two or more compartment pharmacokinetic model without the necessity of using plasma concentration data. They found that most of the 24 patients studied fitted satisfactorily into a two-compartment model and felt that this was encouraging because such a relatively simple

model structure lended itself very well to future identification for online tuning.

Rametti and Bradlow (83) used the data derived from their earlier work (82) to test a number of algorithms designed to provide automatic control of neuromuscular blockade in computer-simulated patients using d-tubocurarine. The algorithm tested first was a PID controller "tuned" to an average patient. This was assessed during two phases - "relaxation" (during which an unrelaxed patient was paralysed to a specific level of T1) and "regulation" (during which it was necessary only to maintain an already induced level of relaxation). Results obtained during the regulation phase were satisfactory given a low level of background noise (the level of which - the writers say - was dependent on the type of force transducer used) but were unsatisfactory during the relaxation phase.

The self-tuning controller of Clarke and Gawthorp was then assessed. This controller worked well at first in all computer simulations. This, however, was in circumstances where the controller was able to issue negative commands (i.e. it was empowered to extract drug from the body at will). Without this remarkable facility there was a significant overshoot in the direction of excessive paralysis at the end of the relaxation phase rendering the system, according to the authors, "unusable"!

Rametti and Bradlow then went on to describe their self-tuning control algorithm. Their aim was to devise a system which, during the relaxation period, would calculate the dose required to achieve the set-point in

the minimum time, without overshoot. Two of the four patient parameters were fixed at mean population values but the other two were explicitly identified on-line. By noting the patient's initial response to the drug, subsequent dosage could be tailored to the individual patient. They found that self-tuning led to most significant improvement in patients who were shown to be resistant to paralysis and felt that the controller which they had described would be quite robust in the clinical setting.

They went on to try out the control system they had devised in 42 patients (84). They measured the mechanical, rather than the electromyographic response, after stimulation of the ulnar nerve, with a strain gauge device. They arranged for the information from this to be fed to an Intel 8088 CPU computer. Paralysis was controlled by regular administration of bolus doses of d-tubocurarine (1 mg ml^{-1}) rather than altering the rate of a continuous infusion.

They gave four reasons for using a bolus-based technique - 1, once the appropriate level of relaxation had been achieved the rate of administration required to maintain it was low and difficult to achieve using simple equipment; 2, if the boluses were sufficiently frequent then drift away from the set-point would be acceptably small; 3, as bolus injections are more frequently used in clinical practice than continuous infusions the authors felt that the bolus technique was more readily acceptable; 4, the group were able to design a simple motor-driven apparatus which could administer rapid boluses as

instructed by the computer. None of these reasons are totally adequate. In six of 42 patients studied the controller failed due to the signal-to-noise ratio being inadequate.

The performance of the control algorithm was described in an accompanying paper (85). The aim of the control algorithm was to evaluate the effect that a bolus dose administered at any time would have on the patient and to continually update this process. Thirty-eight patients were studied (19 aimed at controlling the T4 ratio and 19 at controlling the single twitch response). The results obtained were good and the authors believed that the main improvement on previous work lay in the avoidance of a significant overshoot at any time.

The most recent work by this group (86) described the use of a self-tuning system for use with atracurium in 22 patients. Bradlow, Uys and Rametti used the same control system as described above; again bolus doses were administered rather than a continuous infusion. The single twitch was the controlled variable and the target was 15% of baseline T1. Patients were intubated once this set-point was reached and anaesthesia was subsequently maintained with 70% nitrous oxide in oxygen, 0.5% halothane and 50 ug boluses of fentanyl as clinically indicated. Initially a bolus of 0.1 mg kg^{-1} atracurium was used but this resulted in considerable delay before relaxation was suitable for intubation and therefore a delay before surgery could commence. Subsequently an initial dose of 0.2 mg kg^{-1} was used in an effort to diminish this delay. The results obtained in this study

demonstrated satisfactory control of neuromuscular block in all patients. Three graphs are included to show the response of an average patient and the most and least sensitive. These graphs are interesting in that they reveal quite an undulating degree of block (particularly in the least sensitive patient) although the mean level is close to the target. This unevenness of relaxation can be attributed to the use of bolus doses rather than an infusion. It is interesting that Bradlow's group should go to the lengths of developing a functional self-tuning system and yet rely on a sequence of boluses to maintain blockade.

4. BIRMINGHAM GROUP

Automatic control of neuromuscular blockade has also been studied by a group from Birmingham, Alabama. Ritchie et al (87, 88) reported initially a system using suxamethonium and incorporating a PID controller. Values for proportional, integral and derivative gains were derived from a series of step responses in 10 patients.

They studied 12 patients. Neuromuscular transmission was assessed by the evoked, rectified and integrated EMG. A Grass S48 stimulator was used to stimulate the ulnar nerve at the wrist every 10 seconds. The dose of suxamethonium administered was calculated on a patient-weight basis. The control algorithm initially held the infusion rate steady at 0.1 mg $kg^{-1}min^{-1}$ until the response was depressed to 90% of the baseline: the PID controller was then initiated. This allowed the dose-response relationship to be in the linear phase. When the response was within 1% of the target the proportional and

derivative terms were made equal to zero to prevent the system from responding to small random variations in response. The maximum infusion rate was limited to 0.2 mg $kg^{-1}min^{-1}$.

Anaesthesia was induced with thiopentone 3-4 mg kg^{-1} and maintained with 1% enflurane and 66% nitrous oxide in oxygen. Patients were intubated without relaxant. The target was 20% of baseline and the infusion was terminated after 30 minutes in order to prevent the possibility of inducing phase II block. Ten of the 12 patients proved to be controllable using the algorithm described: the other two were relatively insensitive and did not achieve target despite infusion of relaxant at maximum rate. Recovery from the effects of the relaxant was always rapid. The authors suggested a number of alterations which might improve the control algorithm. These included increasing the initial infusion rate, increasing the ceiling on the infusion rate and switching in the PID controller only when the initial response had been reduced to near zero thus allowing the controller to work in a more linear portion of the response.

These alterations aside, this group have devised an eminently workable system. They suggested that vecuronium might be a suitable agent for controlling in this fashion and that the system might be useful for examining physiological and pharmacological interactions.

A further publication from this group demonstrated the use of vecuronium in an automatic control system (89). A PD controller was used and the set-point was 10% of baseline. A manually controlled group was compared with

the computerised group. It was concluded that although the patients in the computer group took longer to reach target, once this had occurred the deviation from the desired level of evoked EMG was much less.

5. AMSTERDAM GROUP

A Dutch group reported 28 patients in whom neuromuscular blockade produced by vecuronium was controlled by a "bang-bang" system (90). The right ulnar nerve at the wrist was stimulated by an Organon Teknika Neuromuscular Transmission Monitor (NTM). This produced a compound EMG which acted as the input to an electronic device, consisting of three elements. The passive element served as an adaptor between the NTM and a comparator. The comparator had an adjustable reference voltage allowing different preset values to be demanded. The controller comprised a solid state relay and syringe pump. The syringe contained vecuronium 0.4 mg ml^{-1} and the rate of infusion was set at 3 ug $kg^{-1}min^{-1}$.

Patients received a "standard" anaesthetic - premedication was with nicomorphine 7.5-10 mg and haloperidol 5 mg intramuscularly one hour before surgery. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and fentanyl 2.5 ug kg^{-1}, baseline measurements of neuromuscular function were obtained and a bolus of 0.07 mg kg^{-1} vecuronium administered. Intubation was accomplished when the EMG had fallen to 30% of baseline or below, closed-loop control being activated before block had recovered to 16% of control. Anaesthesia was

maintained with 67% nitrous oxide in oxygen, additional doses of fentanyl being given as required.

The results are not furnished in great detail. De Vries states that after the control mechanism was initiated "a depression of neuromuscular transmission was obtained which oscillated around the preset value - in general between 13% and 17% of control ..... twitch heights of less than 10% or more than 25% of control were not observed". No more detailed assessment of the spread of results was given.

In summary this an interesting paper but in fact a less sophisticated control algorithm than that used by any of the four previously noted groups is described. It is interesting that a system of such relative crudity will apparently maintain the level of paralysis at very close to target although, as noted above, no measurement of the spread of results is provided. It seems unlikely that a system of this nature could produce a steady enough level of paralysis to clearly see the effect of any pharmacological perturbation.

6. LONDON GROUP

A recent publication described the control of neuromuscular block with atracurium using a PD system. Webster and Cohen (91) used a Datex neuromuscular transmission monitor (NMT100), one of two portable battery-operated computers (Tandy 100, Epson HX-20) and a Graseby MS16A syringe driver loaded with a 5 or 10 ml syringe containing undiluted atracurium. Their program was written in Microsoft BASIC and caused the computer to

receive information from the NMT every 20 seconds and update the infusion rate every minute.

Twenty patients were studied ranging from a three year old boy having a hypospadias repair to a 33 year old lady with a phaeochromocytoma. A standard anaesthetic technique was used. Patients were premedicated with 5-10 mg diazepam orally and induced with thiopentone 4 mg kg^{-1}. Initial paralysis was achieved with atracurium 0.5 mg kg^{-1} and anaesthesia maintained with 70% nitrous oxide and 0.5% enflurane in oxygen. A target T1 of 10% was used.

The mean level of T1 obtained during steady state was 8.90% with a standard error of the mean (SEM) of 0.47 at a mean infusion rate of 0.45 mg $kg^{-1}hr^{-1}$ (7.5 ug $kg^{-1}min^{-1}$), SEM 0.02.

This again is an interesting piece of work and demonstrates the feasibility of successful control of neuromuscular block in the clinical setting with a relatively simple algorithm. The fact that good control was achieved with such a wide variety of patients demonstrates the robust nature of the system. It would have been interesting if details of how the actuating parameters had been obtained were given and although values for SEM of the mean were provided, there is no indication of the spread of results around the target.

Three further recent publications are worth comment.

Clutton-Brock et al (92) used a feature of the Datex Relaxograph to describe a method for controlling neuromuscular block. The high-output alarm can be set to

respond when the T1 exceeds a preset value. A 5 volt signal is emitted from the output port of the Relaxograph until the T1 falls below the alarm level. This signal can be used to trigger a syringe pump to deliver a short infusion of relaxant. A controlling box of electronics governs the latency of triggering after the signal begins, the duration of the infusion and the period of time between two separate infusions. This mechanism consequently acts as a "bang-bang" type of controller. No mention of any clinical trials is made in the abstract.

A similar device is described in more detail by Wait et al (93). The 5 volt signal mentioned above can be used to switch a small relay and activate the power supply to a syringe pump. Eleven patients were studied. Non-standardised anaesthetic techniques were used as the objective was to assess the performance of the system under a variety of conditions. A bolus of atracurium 0.5 mg kg^{-1} was given after calibration of the Relaxograph. In all but two cases this caused the T1 to decrease to zero (in these patients a further 10 mg of atracurium was given). The loop was closed before the T1 had recovered to the preset level and an intermittent infusion of atracurium (5 mg ml^{-1} in 0.9% saline) was therefore controlled by the relay. Satisfactory surgical relaxation was achieved in all patients.

The systems described in these two publications can provide perfectly acceptable clinical neuromuscular block. The nature of the systems is such, however, that the degree of block will always follow an oscillatory pattern. This limits the usefulness of these devices as research

tools since a totally steady level of block cannot be achieved and, therefore, the effect of minor changes on the control system are likely to pass undetected. Nevertheless, these methods combine the virtues of safety and simplicity.

A recent abstract in Anesthesiology (94) described an adaptive system for the administration of vecuronium. Forty patients were studied and the workers concluded that a constant and adequate level of relaxation was reached rapidly and subsequently maintained within narrow limits.

CHAPTER 4

EQUIPMENT

This chapter outlines the equipment used in the investigations described later in this thesis.

1.THE DATEX RELAXOGRAPH

The Datex Relaxograph (fig. 6) is an electromyographic monitor of neuromuscular function. It is a modification of the neuromuscular transmission monitor of the Datex Anaesthesia Brain Monitor (ABM) and works by electrically stimulating a peripheral nerve and recording and demonstrating the resulting integrated EMG response. The ulnar, median or posterior tibial nerves may be stimulated.

For our work we used exclusively stimulation of the ulnar nerve at the wrist. Five electrodes are used - two for stimulation, two for recording and one to act as an earth. The two stimulating electrodes are placed over the appropriate nerve; only one electrode need be placed over the appropriate muscle due to the differential amplification employed by the Relaxograph but the other recording electrode must also be attached. It is recommended that the earth electrode be placed between the stimulating and recording electrodes in order to minimise the stimulus artefact (the response coming directly to the measuring electrodes from the stimulating electrodes).

The EMG response is gated - the electronic integration lasts for 10 ms, beginning 3 ms after the nerve is stimulated - this prevents incorporation of the stimulus artefact into the recorded EMG response. The resulting EMG is amplified, rectified and integrated. The

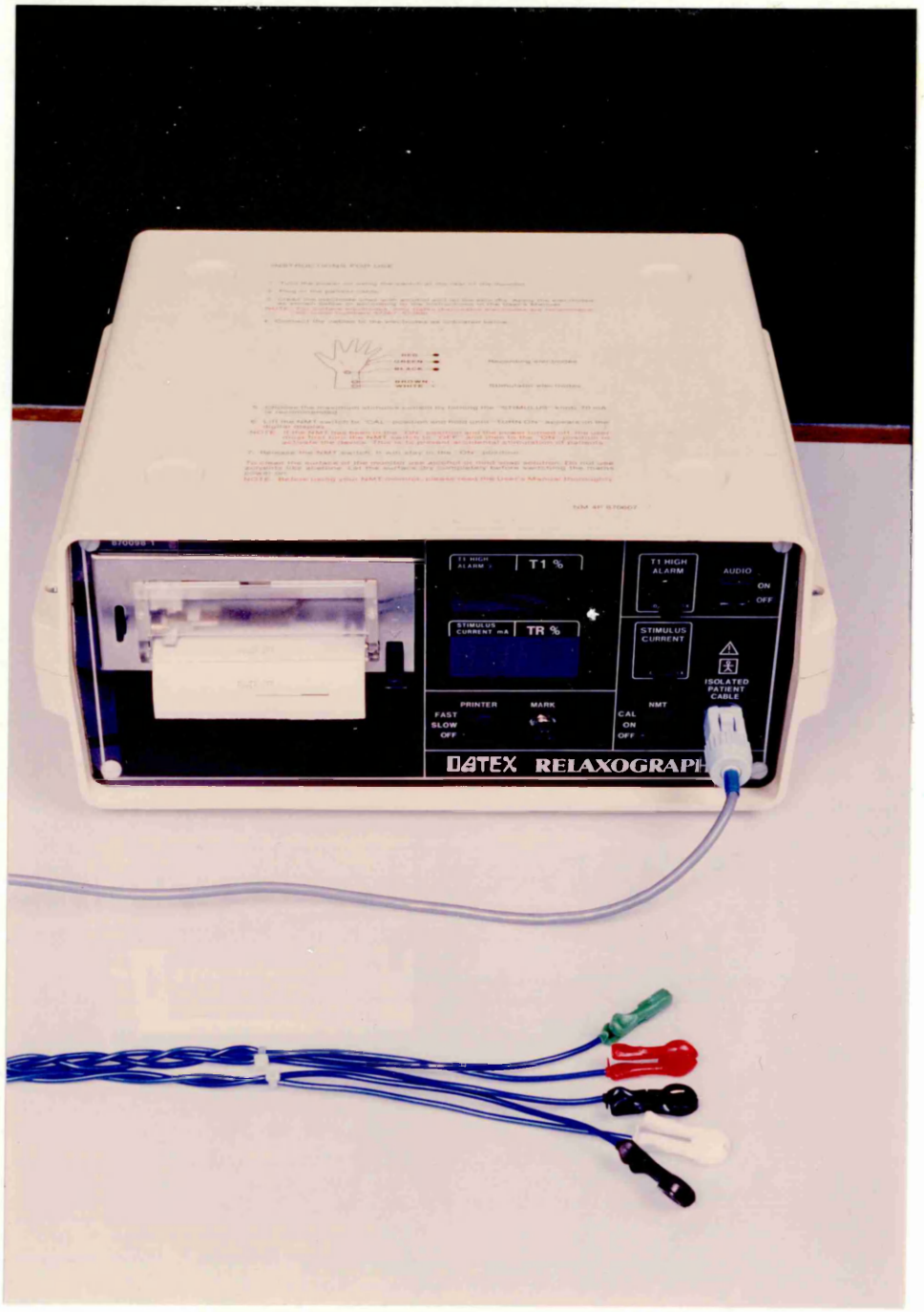


Figure 6. Datex Relaxograph

machine uses a fully isolated constant current stimulator which produces ToF stimuli every 20 seconds with a pulse width of 100 us and a frequency of 2 Hz.

Calibration should be carried out after anaesthesia is induced but before the administration of any relaxant drugs. Calibration involves the machine searching for the stimulus current required to activate all the fibres of the innervated muscle. Once this has been achieved the Relaxograph increases this current by about 20% producing a supramaximal stimulus current. Once the supramaximal current has been established, four stimuli are delivered to set the 100% reference values. At 20 second intervals the device displays the T1 (expressed as a percentage of the baseline) and the TR (the ratio of the fourth twitch to the first expressed as a percentage). When less than four responses are elicited the TR is replaced by a number of dots representing the number of responses which can be detected. As well as being displayed every 20 seconds, the results are printed out by the Relaxograph. Two speeds are available: one prints all four responses after every recording and the other only the first and fourth responses at 80 second intervals.

A typical printout from the Relaxograph provides details of the calibration values - gain, supramaximal stimulus and stimulus artefact. The tracing of the degree of neuromuscular block itself has a time scale printed on it at 15 minute intervals in the case of the slow printout and five minute intervals in the case of the fast printout. The Relaxograph also has another useful facility - an event marker. The control panel of the Relaxograph

includes a small button which, when pressed, marks the tracing with a number. Thus, a mark can be made at the time of, for example, a bolus injection of another drug. This enables the tracing to be analysed subsequently with exact knowledge of the time at which any change was made.

A further feature of the Relaxograph is the T1 high alarm which can be set to trigger at any value of T1 between 0-100% of the reference value. When the set figure is exceeded visual and audible (silenceable) alarms commence and a potential of 5 volts appears at the appropriate pin of the analogue output socket of the machine. Wait et al (93) have adapted this feature to allow on-off control of blockade as described earlier.

Carter et al (57) compared the results obtained from the Relaxograph with those from a Gould-Statham force transducer. Simultaneous measurements were made on the same patient using the same arm, i.e. electromyographic and mechanical responses to the same stimulus were recorded during onset and offset of paralysis induced by atracurium. Comparison of the mechanical and electromyographic results for T1 yielded a correlation coefficient of 0.933. This study concluded that the Relaxograph provided a reliable assessment of neuromuscular function but did point out some potential disadvantages. In obese patients the positioning of the electrodes is crucial if the machine is to successfully produce a supramaximal current. Occasionally electrode drift or instability occurs, the cause of which is not clear. Fixation of the hand is important (although not as vital as when a force transducer is used) because changes

in the relative positions of the recording and stimulating electrodes could alter the measured evoked response. It may be that the most important factor in this potential instability is alteration in electrode impedance which increases with time and with changes in temperature.

2.THE VICKER'S TREONIC IP3 DIGITAL SYRINGE PUMP

This pump (fig. 7) was used to provide an appropriate infusion rate of dilute atracurium throughout the study. It is a well established, reliable pump. A Plastipak 50 ml syringe is driven by a stepping motor and the infusion rate is controlled digitally in steps of 0.1 ml hr^{-1}. Safety mechanisms include an audible and visible alarm to indicate outlet occlusion or power failure (95).

Normally the pump is operated by three controls: the pump stop/start selector, the flow rate selector (which allows any infusion rate between 0.1-99.9 ml hr^{-1} in 0.1 ml steps to be selected) and the carriage release which allows manual carriage movement by disengaging the driving pinion. The pump is known to be accurate throughout its range to within 0-2% of its set-rate (96).

3.RML 380Z-D MICROCOMPUTER

This is one of the 380Z series of microcomputers produced by Research Machines Limited (fig. 8). It has a double disc drive and is compatible with either single or double density 5.25 cm discs.

Software for the 380Z-D is organised at three levels. The first level contains routines that are stored permanently in its read-only memory (ROM), so-called firmware. The second level is a set of routines that are

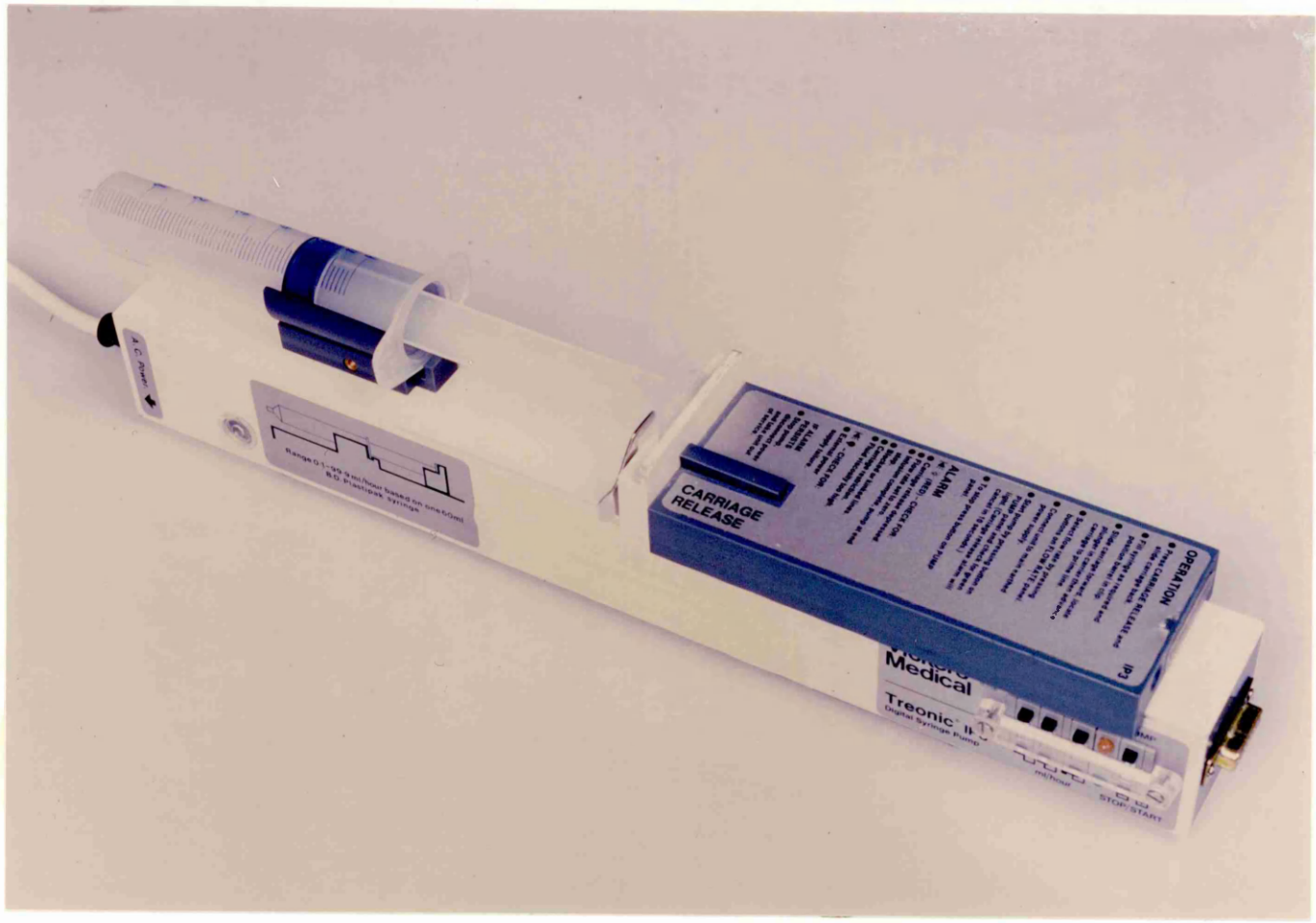


Figure 7. Vicker's Treonic IP3 Syringe Pump

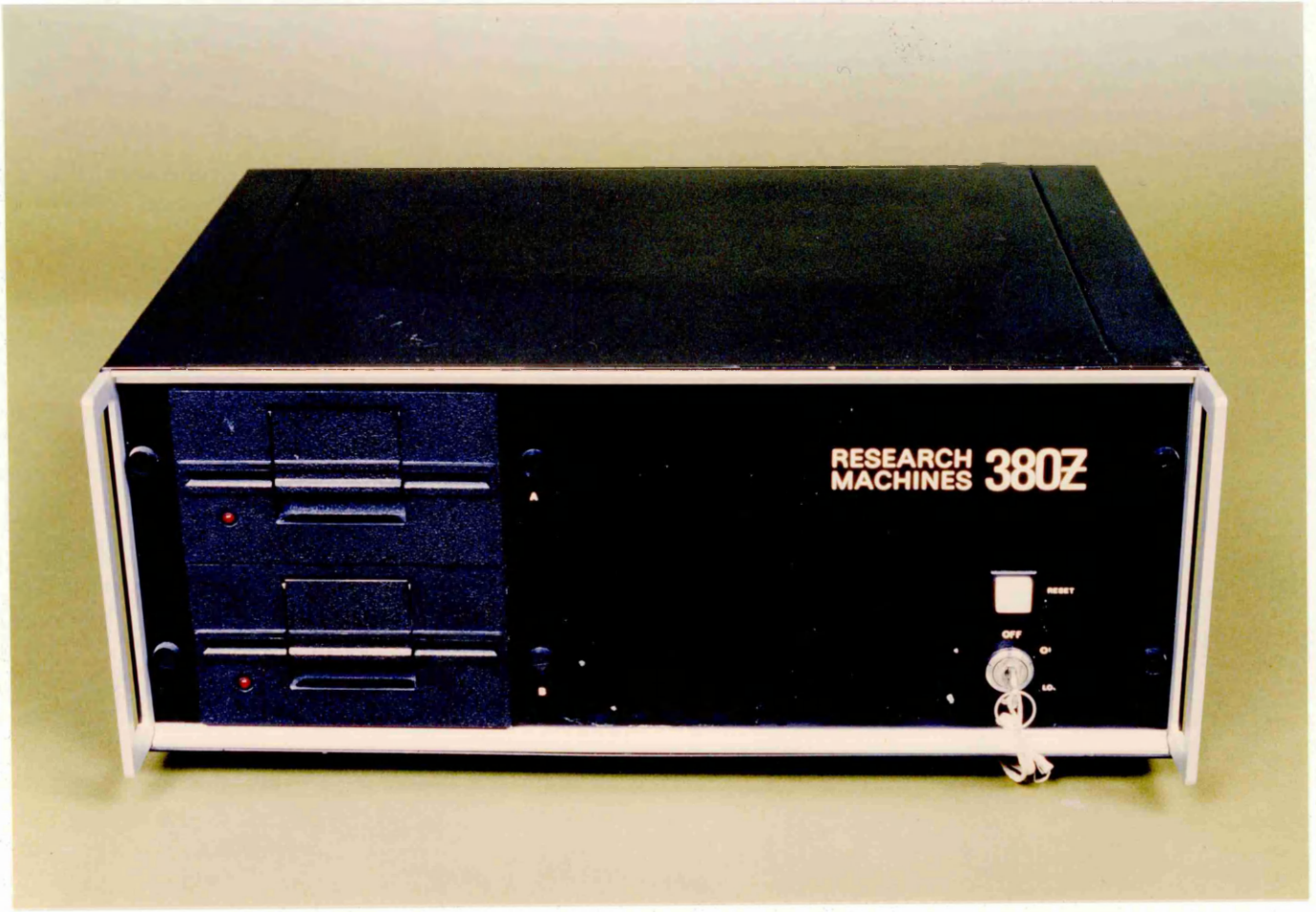


Figure 8. Research Machines Ltd. 380Z-D Microcomputer

maintained on a special (system) disc. Some of these are loaded into the computer's memory at the start of each working session - a process known as booting; others are loaded only when required. The third level includes the programming and language facilities and general purpose application packages (such as the word-processing program WordStar, with which this thesis is written).

Firmware controls the internal operation of the computer hardware and is known as the Central Operating System (COS). COS interprets and obeys commands entered from the keyboard, controls operation of the peripheral devices (printer, keyboard etc.) and initiates the loading of an operating system from disc storage. This level of software is activated whenever the computer is switched on or the Reset button pressed.

System software is based on CP/M (Control Program for Microcomputers) which acts as an interface between the user and the computer.

A keyboard, visual display unit and printer (Epson MX-80 III) are all appropriately interfaced to the microcomputer.

4.INTERFACES

a.Interface to Relaxograph

The output data from the Relaxograph are in RS-232C serial format and are transferred to the computer by way of the standard serial port. The data are presented as a character string (in ASCII format) with each set of data consisting of 41 characters including commas, line feed and carriage return. The structure of the character string and the interconnection details are shown in Appendix II

of the Relaxograph manual. The speed at which the computer reads the data has to be matched to that at which the data is transmitted. This is done by temporarily defining the serial port as the printer port and setting it up at the correct speed. The BASIC command is "PRINTER 4,1", which sets the serial port to the required speed of 300 baud (bits per second). The data are read from the Relaxograph data buffer by means of an INPUT LINE statement.

b.Interface to syringe pump

This account should be studied in conjunction with the circuit diagram for the IP3 (fig. 9).

For conventional use, the speed of the pump is set by means of the thumbwheel switches S2, S3 and S4 (S1 being the pump drive on-off switch). The tens are set on S2, the units on S3 and the decimals on S4. Each switch produces a decimal digit between 0 and 9 in binary coded decimal (BCD) form. Thus, each has four output pins, one for each of the four bits required to represent a decimal digit (2^0, 2^1, 2^2, 2^3). If a bit is set, a 12 volt signal appears at the appropriate pin; if it is not set, zero volts appear. The BCD signals from the switches pass to rate multipliers (three altogether, one for each switch: Q3, Q4 and Q5), which control the pump's timing circuitry to provide the speed corresponding to the switch settings.

The pump used in this project has been modified to allow the BCD signals which control the rate multipliers to be provided by the computer, rather than by the thumbwheel switches. The modification is simple, consisting of a 15-way D connector fitted to the pump

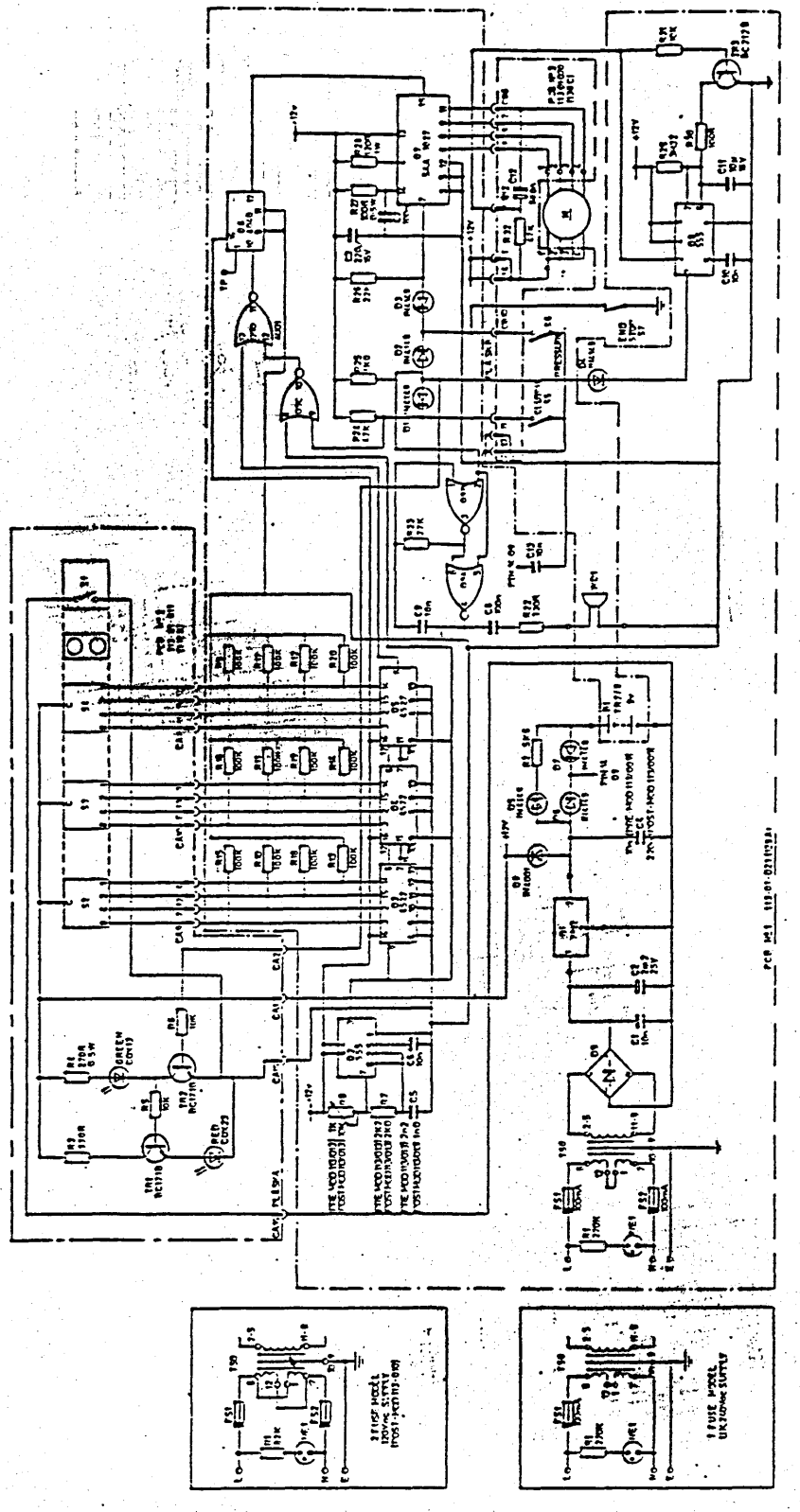


Figure 9. Circuit diagram

Vicker's Treonic IP3 Syringe Pump

case, and wires connecting 13 pins of this connector to the BCD connector inside the pump. Twelve of these wires go to the pins of the BCD switches, while the other wire is connected to the pump's 12 volt supply. The 15-way socket is connected to the computer which routes the 12 volt signal to the appropriate pins on the BCD switches under software control. The signals from the computer are physically supplied by a special interface board, which consists of Research Machines' PIO/RTC development board with some added circuitry. A brief description of the operation of this board is now given.

The board contains three Z80 PIO (parallel input/output) chips and a CTC (counter timer circuit) chip, which provides a real time clock (RTC) facility. For the present project, only one of the PIO chips is used and the CTC chip is not used. The PIO chip contains two 8-bit ports (A & B) and these are configured as output ports during the initialisation of the board by the main program. When a particular pump speed is required, the program peels off the tens, units and decimals and sends each digit, in BCD form, to four pins of the PIO ports. The decimal bits go to pins A0 to A3 (with A0 being the lower bit, i.e. 2^0), the units to pins A4 to A7 and the tens to pins B0 to B3. Each group of four BCD bits then goes to an optical isolator, which is arranged so that, when a particular input bit is set, the corresponding output pin is connected to the 12 volt supply. The output signals from the optical isolators, which are still effectively three BCD digits, are then passed to the BCD connector in the pump, as described above.

It is important to remember that when the pump is under computer control, the thumbwheel switches must all be set to zero otherwise the rate multipliers in the pump will receive signals from both the computer and the switches, and any bit which is not set by the computer but set by the switches will be treated as if it were set, and will contribute to the output speed.

SOFTWARE

Two programs were written for use with this project. The first was used for implementation of the control algorithm, while the second was a program designed for analysis of the data collected (see Appendix 1). Both were written in BASIC 6G2.

The implementation program begins with some general remarks defining the purpose of the program, the names for the various variables and the dimensions of the array for the storage of data. The program then defines the initial values for the proportional and integral gains. The initial time is measured by the output from the Relaxograph. The printer is engaged and the operator is requested to input details for the identification of the patient as well as details to help with the running of the program, e.g. the patient's weight (both proportional and integral gains are weight-dependent). These details are printed out at the beginning of each run for each individual patient. The program checks to see if the constructed filename already exists on the data storage disc. If not, the program asks for details of the concentration of atracurium and the desired degree of neuromuscular blockade. This information is then printed

out along with the values for proportional and integral gains and the headings of the continuous printout - COUNT, TIME, T1, INT, SPEED and MARK. The VDU then indicates that the program is ready to commence automatic control and this is initiated by typing "R".

The next stage of the program concerns the automatic control loop which at this point is open. It is closed by typing "C". The program then looks at the output from the Relaxograph and the relevant output values (time, T1, TR, Mark) from this are stored in an array. The next step is to calculate the speed of the pump from the T1 data and the gains and to implement this flow by means of a PROC statement. The following data then appear on the VDU screen and are printed out. COUNT, T1, IN, SP, MARK and the status of the loop (open or closed).

This section of the program (from the closing of the control loop) is repeated every 20 seconds until a different command is issued - normally one requesting storage of data on the data disc. The values for the TIME, T1, IN, SP and MARK are then stored and the program comes to an end.

The analysis program is relatively simple. Again, the program begins with definitions of the various parameters which are subsequently used for the calculation of various indices. The data run is identified initially by the program asking for the filename. The data from the corresponding array is fed into a file to allow analysis. The program then asks for the first and last record numbers of the period on which analysis is to be carried out. By incorporation of a FOR-NEXT loop the variables in

the array are subjected to a variety of arithmetic manoeuvres. After this values for mean level of block, standard deviation and coefficient of variation; dose over controlled period; point count and root mean square deviation (see later) are calculated by appropriate equations.

The foregoing has described the equipment used for the studies carried out in this thesis. Fig. 10 shows how the components were neatly stored on a folding two-tiered trolley. This simplified the process of transferring the equipment between theatres and, indeed, between hospitals.

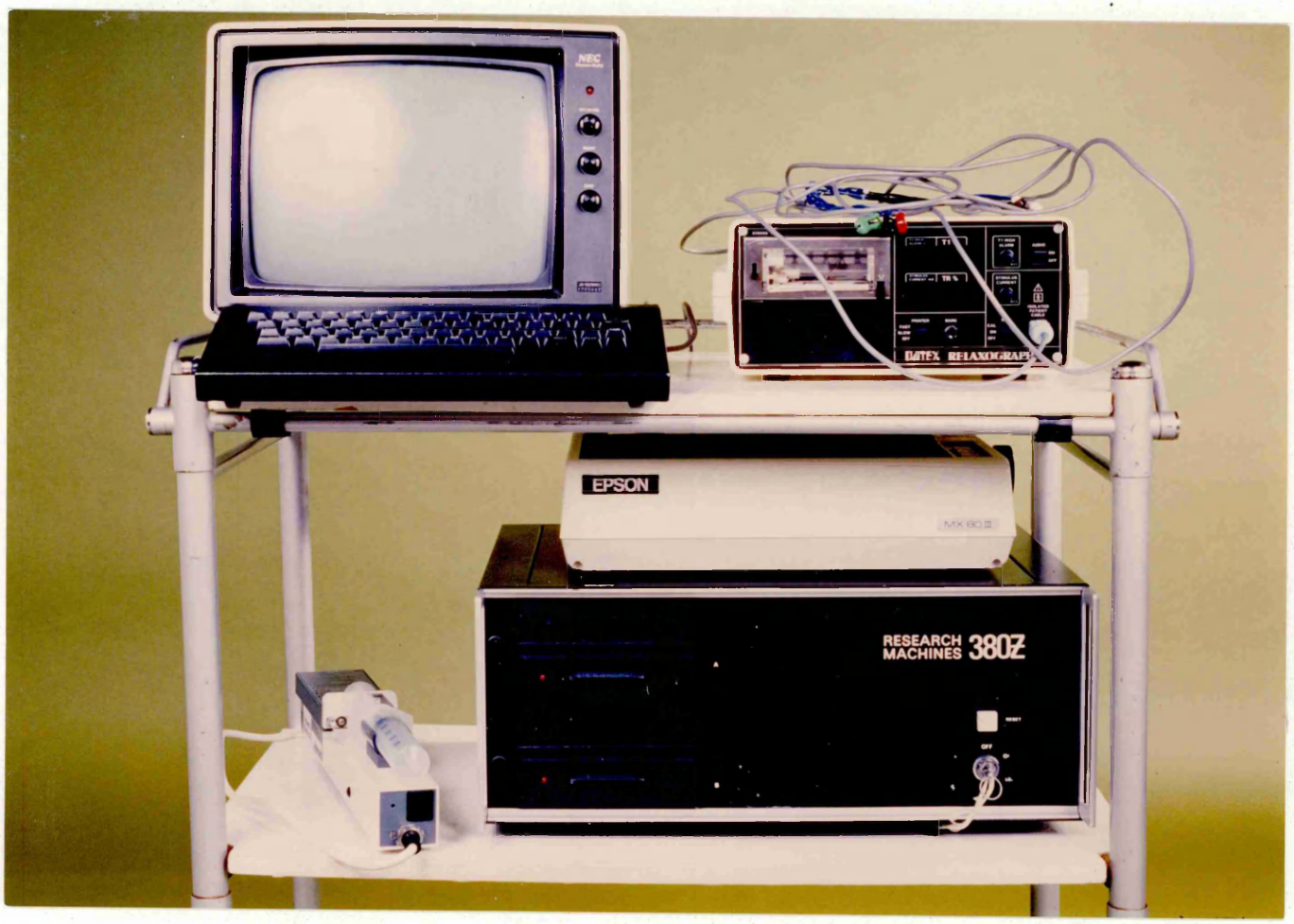


Figure 10. Arrangement of equipment for use in theatre

CHAPTER 5

1.STEP TESTS

Introduction

Before an automatic control system can be used it is necessary to derive appropriate controlling parameters. This can be done by applying simple tests to a sample group of patients and using the derived values in the design of the automatic controller. The work described in this chapter was therefore an essential preliminary step to the main project and was carried out to obtain parameter values for the controller.

The classic rules relating to setting of gains for automatic controllers were laid down in 1942 by Ziegler and Nichols (69). They are strictly designed for use in circumstances where a model is available and amenable to a few simple experiments. As outlined in the chapter on control engineering, non-adaptive controllers may have up to three components - proportional, integral and derivative.

Two approaches were described by Ziegler and Nichols. The one used here requires analysis of a "process reaction curve". This is obtained by applying a sudden sustained change to the input of a system. In these circumstances a pen recorder at the output of the system will trace an S-shaped curve (fig. 11). Examination of this curve will give values for proportional, integral and derivative parameters, as described below.

In our experiments, this meant infusing a dilute solution of atracurium to a patient at a constant rate

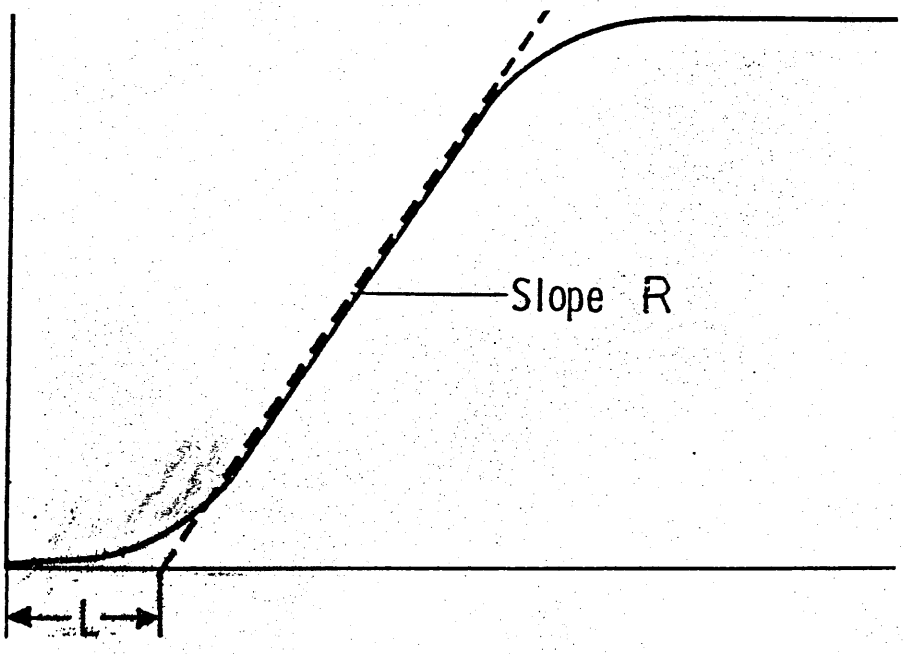


Figure 11. Process Reaction Curve
(After Ziegler and Nichols)
R - slope
L - lag time

until a steady level of neuromuscular block was achieved, then altering the infusion rate (either up or down) and waiting until a new steady state was reached. The steady states achieved should in neither instance pass into saturation, i.e. the T1 must not reach either 0% or 100% of control. This presented a number of logistic problems which will be described below. Analysis of the Relaxograph traces allowed calculation of proportional and integral gains for the automatic controller.

Methods

Three patients were studied. None had neuromuscular disease and none was receiving medication likely to affect neuromuscular transmission. Hospital ethical committee approval was obtained. All patients were ASA I and all were undergoing the same operation - mastectomy and axillary clearance.

Premedication was with oral temazepam 20 mg, 90 minutes before surgery. All patients were anaesthetised in theatre. Pre-operatively the patient's blood pressure was checked and ECG electrodes attached. A 16 gauge cannula was inserted into a suitable vein in the forearm under local anaesthesia.

The patient was also connected to the Datex Relaxograph. This involved initially gently abrading the skin over the proposed site of electrode attachment with an alcohol soaked swab and then carefully drying this area with further swabs to leave a clean, dry region. The electrodes were then attached and secured with adhesive tape. Initially Datex electrodes, designed specifically for use with the Relaxograph, were used but standard ECG

electrodes proved equally suitable. The patient's arm was then immobilised in a wrist splint (fig. 12) and the splint secured to an armboard which was then abducted to 45-90^{o} depending on the proposed operation. Surgeons were counselled as to the importance of the arm remaining immobile for the duration of the case.

Anaesthesia was induced with fentanyl 1-2 ug kg^{-1} and thiopentone 3-4 mg kg^{-1}. After induction, calibration values were obtained with the Relaxograph. During this period the patient was allowed to breathe spontaneously 66% nitrous oxide in oxygen supplemented by 1% enflurane. Laryngoscopy was carried out without muscle relaxation and intubation was facilitated by the application of lignocaine spray to the cords. Intubation was successfully accomplished in all three patients.

Following intubation, automatic pulmonary ventilation was commenced and anaesthesia maintained with 66% nitrous oxide and 1% enflurane in oxygen supplemented by boluses of 50 ug fentanyl as indicated.

The Relaxograph tracings were obtained in the following fashion. A bolus of atracurium was given with the intention of achieving a level of block with an approximate T1 of 50% (0.15 mg kg^{-1}). Once this had occurred, an infusion of atracurium (0.5 mg ml^{-1} in 0.9% saline) was commenced with the aim of maintaining this steady level (4 ug $kg^{-1}min^{-1}$). After a period of steady paralysis a step change in the infusion rate was made, again avoiding saturation, and the situation observed until a new constant level of block was obtained.

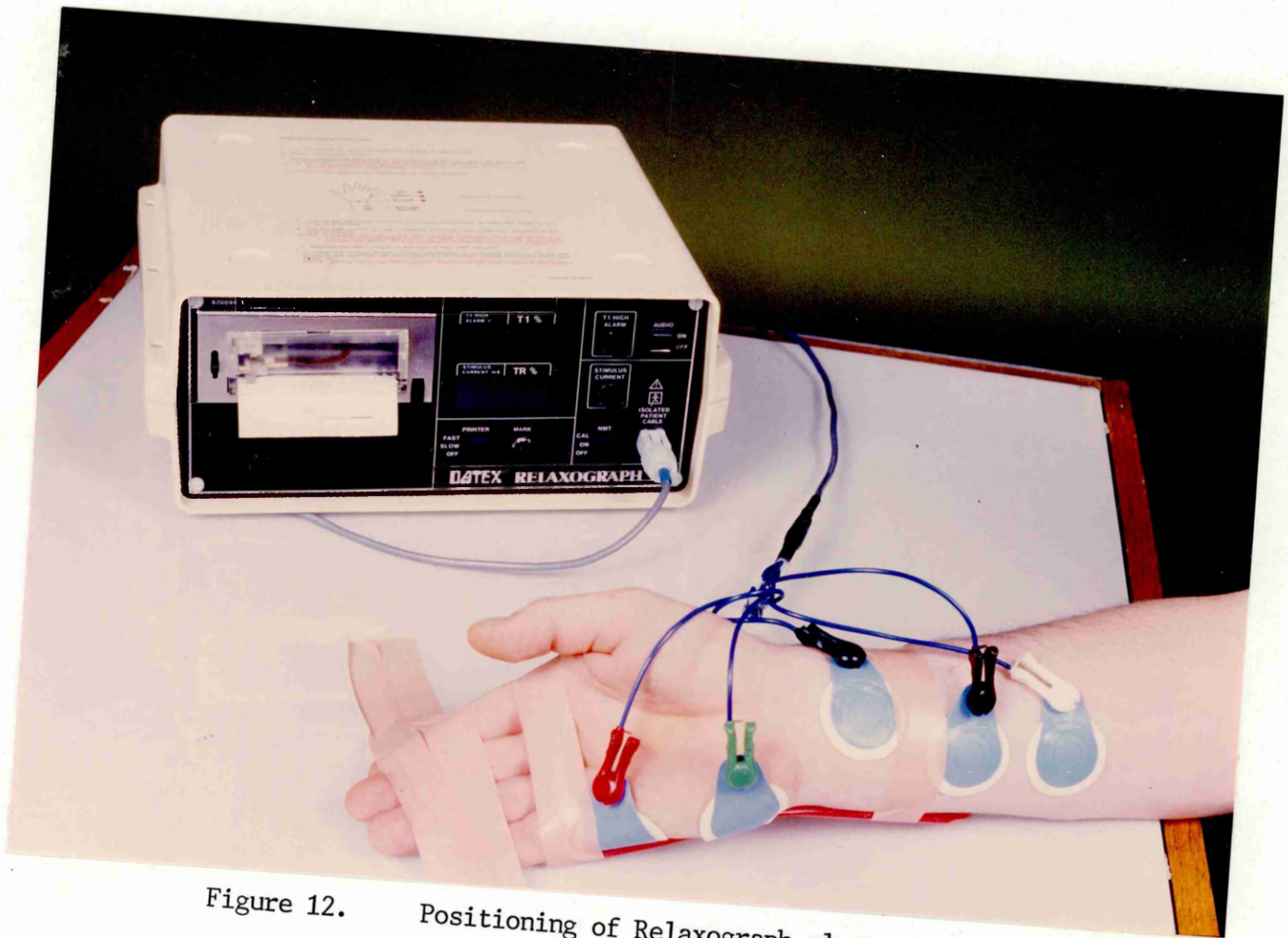


Figure 12. Positioning of Relaxograph electrodes

As the end of surgery approached enflurane was discontinued, the atracurium infusion stopped and neostigmine 0.05 mg kg^{-1} together with atropine 0.02 mg kg^{-1} injected. When the T1 had reached 70% of baseline, automatic ventilation was discontinued. Extubation was carried out when an adequate tidal volume had been re-established.

Results

Three step tests were carried out. Figure 13 illustrates a representative specimen. These traces are equivalent to process reaction curves and are analysed by means of the Ziegler-Nichols rules, as described by Power and Simpson (70).

A tangent is drawn through the point of inflection of the S-shaped curve and the slope R measured (as shown diagramatically in fig. 11). The intercept of the tangent with the time axis gives the lag-time, L. Figure 13 shows how this process is applied to the Relaxograph trace.

Ziegler and Nichols suggest the following controller settings from a curve of this sort:

For P control $K_p = \Delta F/RL$;

For PI control $K_p = 0.9\Delta F/RL$, $K_i = 0.3/L$ per min.

where K_p is the proportional gain, K_i the integral gain, ΔF the step change in the input (i.e. the alteration in the infusion rate), L the lag time and R the slope of the process reaction curve.

The results from all three patients were remarkably similar. The derivation of the values from case 1 will be demonstrated here.

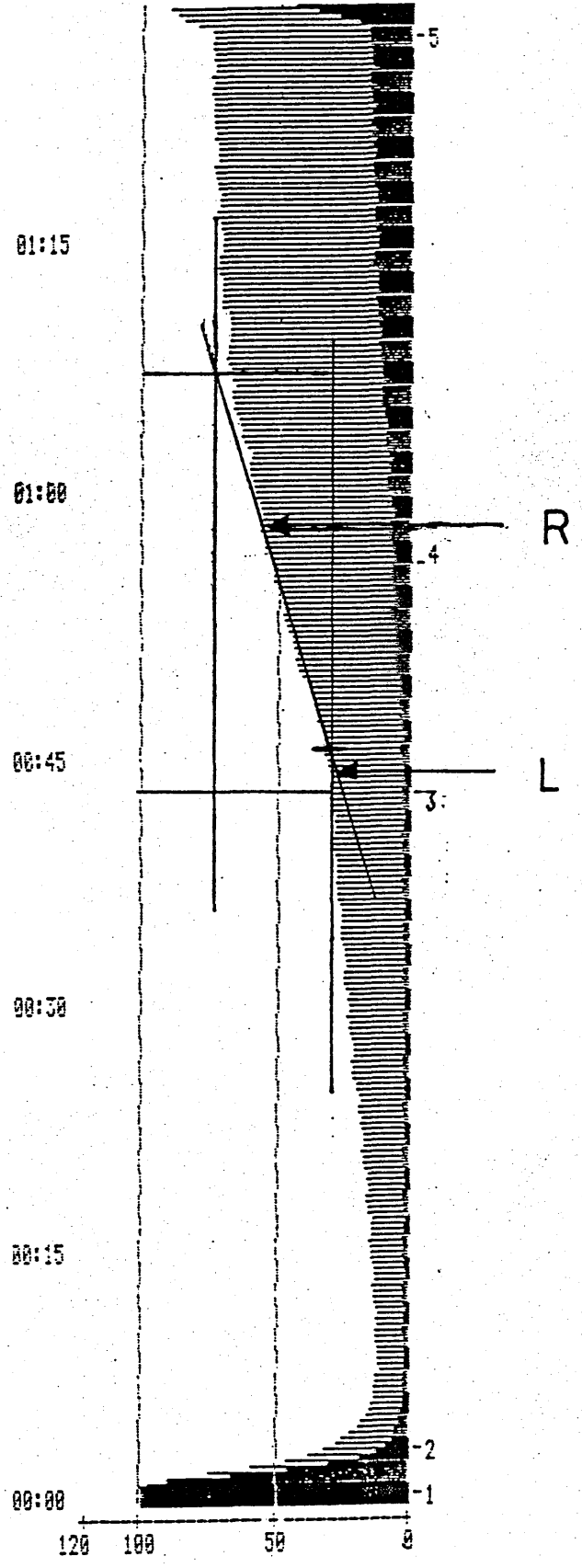


Figure 13. Application of Process Reaction Curve to Relaxograph trace

Case 1:

Weight 58 kg, Bolus dose 9 mg,

Initial infusion rate 28 ml hr^{-1},

Final infusion rate 21 ml hr^{-1}.

L = Lag Time = 2.6 minutes.

R = Slope = 45% / 22.7 minutes.

ΔF = Step change in input = 7 ml hr^{-1}

$K = \Delta F/RL = 22.7 \times 7 / (45 \times 2.6) = 1.36$ ml hr^{-1} $\%^{-1}$

The gain values in this study are all weight-related. Consequently this value must be divided by the patient's weight in order to provide an index figure.

For P control, then K = 0.023

For PI control, $K_p = 0.023 \times 0.9 = 0.021$

and $K_i = 0.3 / 2.6$ per minute = 0.115.

Dividing this figure by three (Relaxograph readings taken every 20 seconds) and then by 58 (patient's weight in kilograms) gives a final value for K_i of 0.0007.

Analysis of the other two tracings gave mean overall values as follows:

$\underline{K_p} = \underline{0.02}$; $\underline{K_i} = \underline{0.0007}$.

Following derivation of these proportional and integral gains, the appropriate values were incorporated into computer programs which were designed to control the

patient's T1 at 20% of baseline. A controller using simple proportional control was assessed first.

2.PROPORTIONAL CONTROL

Introduction

Only one patient was studied whose neuromuscular block was controlled by a simple proportional controller. The reasons for this will subsequently become clear.

Methods

The patient studied was an otherwise healthy female aged 65, weighing 54 kilograms and undergoing right mastectomy and axillary clearance.

Premedication was with temazepam 20 mg, 90 minutes pre-operatively. As in the step tests, anaesthesia was induced in theatre following connection of ECG electrodes, blood pressure cuff and Relaxograph electrodes. Induction was with fentanyl 1-2 ug kg^{-1} and thiopentone 3-4 mg kg^{-1}. After induction the patient was allowed to breathe spontaneously 66% nitrous oxide and 1% enflurane in oxygen. At this point, calibration values for the Relaxograph were obtained and then a bolus of 0.25 mg kg^{-1} atracurium was administered. Once the T1 had fallen to 25% of baseline (49) the trachea was intubated and automatic pulmonary ventilation commenced. The initial bolus caused the T1 to fall to 7%. From this point spontaneous recovery was allowed to occur until the T1 had reached 20% and then the automatic controller was switched in and the controlled infusion of atracurium (0.5 mg ml^{-1} in normal saline) started.

The control algorithm then adjusted the flow of atracurium in the following manner. The Relaxograph recorded the patient's T1 every 20 seconds. This data was transmitted to the computer where the flow of atracurium was calculated by means of a simple equation involving the proportional gain, the patient's weight and the error (the difference between the current value of the T1 and target), thus:

$$\underline{\text{FLOW (ml hr}^{-1}\text{)}} = \underline{K_p} \times \underline{\text{weight (kg)}} \times \underline{\text{error}}$$

This process was updated every 20 seconds during the period that the controller was in use, i.e. the rate of the infusion was adjusted three times a minute.

Anaesthesia was maintained as described in the section on step tests. Toward the end of surgery, enflurane was discontinued and the atracurium infusion stopped. Reversal of neuromuscular block was achieved with neostigmine and atropine and once adequate spontaneous breathing had been re-established the trachea was extubated.

Results

The Relaxograph tracing obtained from the single trial with a proportional controller is illustrated in fig. 14. Cursory inspection of this trace indicates that while the degree of blockade achieved is relatively constant, there is a considerable discrepancy between the target and the actual level of block obtained.

A steady state was deemed to have occurred when the T1 had stopped increasing and stabilised at a constant level, in this instance just before half an hour had

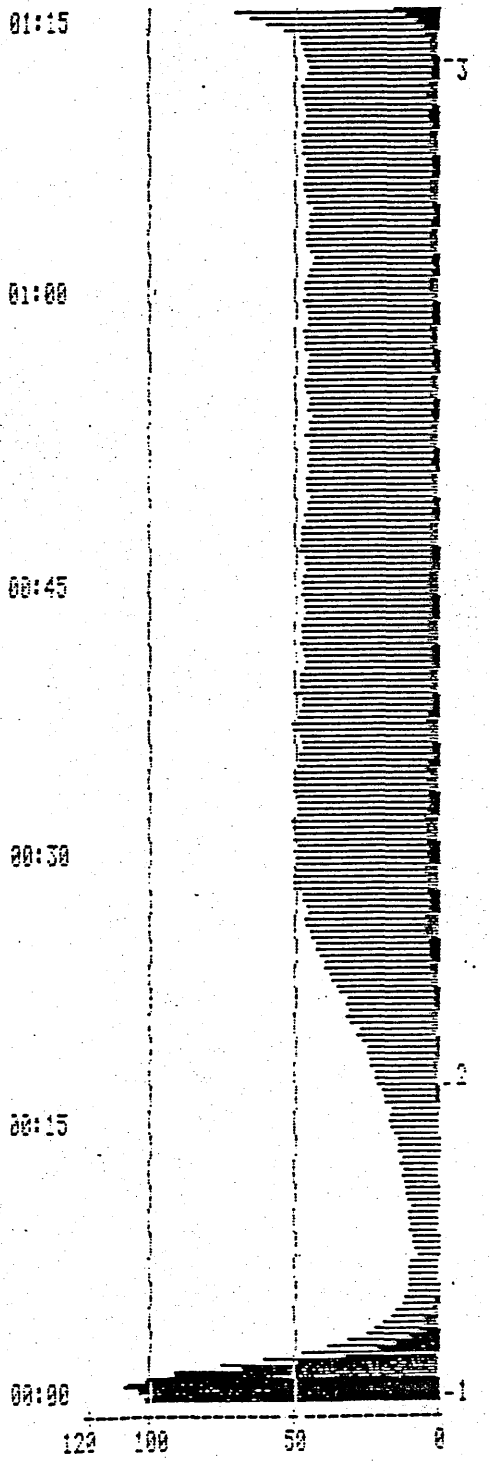


Figure 14. Relaxograph trace obtained using P control

elapsed from the beginning of the trace. The data produced were analysed for the following features after a steady level of blockade had been achieved: mean level of T1, standard deviation, coefficient of variation; duration of controlled period; atracurium dosage; point count (PC) and root mean square deviation (RMSD).

The last two of these require further explanation. The PC is the number of points lying above the target T1 of 20% during the controlled period and the RMSD is the root mean square deviation of the points around the target. It is calculated as follows. Each value of T1 during the controlled period is analysed. The difference between this point and 20% is squared (in order to eliminate negative values). All these values are summed and this figure is divided by the total number of observations. The square root of this number is then taken to give the definitive value for the RMSD:

$$RMSD = \sqrt{[\sum(T1\text{-}target)^2 / n]}$$

The RMSD is consequently analogous to the standard deviation but differs in that it gives a measure of the dispersion of points around the target rather than around the mean. These two indices (PC and RMSD) should be treated together - ideally, in the case where the measured T1 remains at the target, the PC would be zero and the RMSD would be 50%. Their use is, therefore, as a measure of the quality of control.

The results for this patient are summarised in table 2.

Table 2. Results - P control.

Duration Controlled Period (min)	41
Mean T1 (%)	46.8
Standard Deviation	1.5
Coefficient Of Variation	3.3
Dose Over Controlled Period (ug $kg^{-1}min^{-1}$)	4.5
PC (%)	100
RMSD	26.8

Discussion

These results demonstrate two of the classical features of simple proportional controllers with an appropriately set gain. Firstly, the stability of control obtained is very good; secondly, there is a considerable offset from the target (in this instance some 27%). It is also a recognised feature of proportional controllers that, although there is always an offset, the margin of this offset (which depends on the proportional gain) cannot be accurately predicted (69, 81). For this reason it is unlikely that automatic control with a simple proportional controller will ever prove entirely satisfactory in the clinical setting - some forms of surgery demand a degree of muscle relaxation which cannot be guaranteed by this sort of system.

This phase of the work demonstrated the feasibility of achieving a constant degree of neuromuscular relaxation using a proportional controller. Although the relaxation achieved reached a steady level there was, however, a considerable offset from the target. It seemed likely that the addition of an integral component to the control algorithm would help to eliminate the offset, albeit increasing the likelihood of instability. For this reason and also because of the large offset in the single patient studied, it was not considered useful to study any further patients in whom simple proportional control was employed. For the next phase of the project, consequently, a proportional-integral (PI) controller was used.

3.PROPORTIONAL-INTEGRAL CONTROL

Introduction

In an attempt to eliminate the offset described in the previous section, the next step was to assess a PI controller. Again only one patient was studied.

Methods

The patient was a 66 year old female, weighing 57 kilograms, and undergoing surgery for breast carcinoma. The anaesthetic technique employed was identical to that used in the previous patient. Once again the controller was implemented when spontaneous recovery of the T1 had occurred to 20%.

In this instance the flow of atracurium was calculated by the PI algorithm at 20 second intervals in the following way:

$$\text{FLOW (ml hr}^{-1}) = [K_p \times \text{wt} \times \text{error}] + [K_i \times \text{wt} \times \Sigma\text{error}]$$

where K_p is proportional gain, K_i is integral gain, wt is patient's weight in kilograms and Σerror is the cumulated error.

Results

The Relaxograph tracing from this patient is shown in fig. 15. The features of interest are first that following implementation of the controller there is a considerable overshoot in the value of T1 above the target to a maximum value of about 42%. After this the T1 gradually falls and toward the end of the run the degree of block appears to be settling out at a value very close to the target. Formal analysis of this period was not

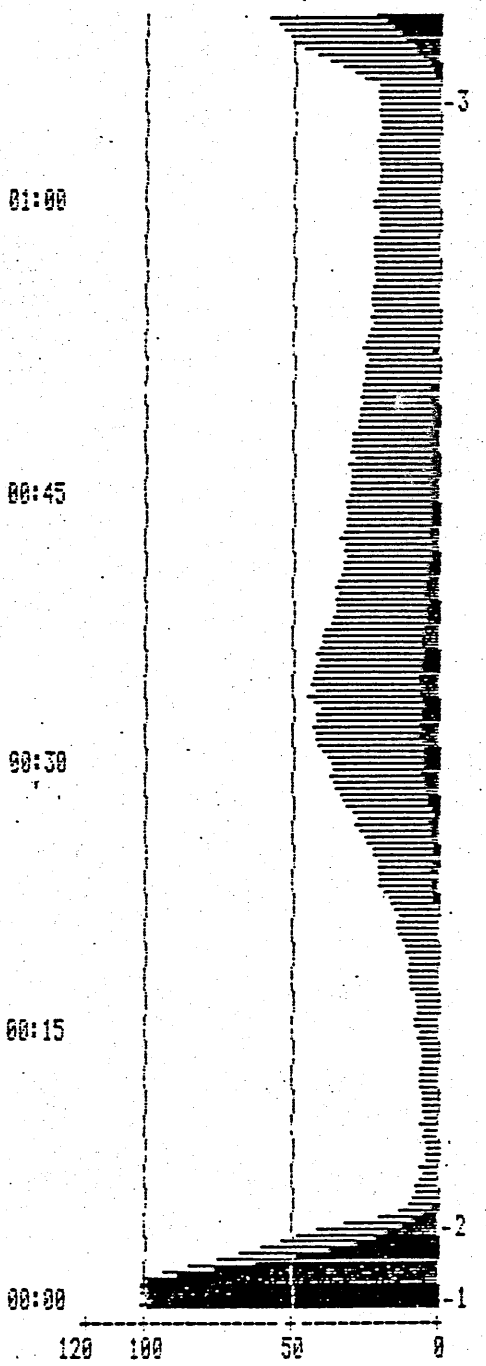


Figure 15. Relaxograph trace obtained using PI control

carried out because the time for which the T1 was close to the target was very short. It seemed likely, however, that the controller would hold the target adequately from this point on.

Discussion

As anticipated the use of a PI controller eliminated the steady state error and allowed the system to satisfactorily achieve the target. One important problem remains, however, and that is the large overshoot which occurs after implementation of the controller.

When control begins the infusion rate is calculated by the PI algorithm, as outlined above. If the controller is implemented when the T1 is at target the initial infusion rate will be zero. This is because there is no error. Only when the T1 exceeds the target will the infusion start. At first the infusion will be driven predominantly by the proportional term (because the proportional gain is so much larger than the integral gain) but as the integral accumulates with time it becomes the most important factor in determining the infusion rate. When the T1 has returned to target after the overshoot, the infusion is being driven solely by the integral.

One potential solution to the problem of the overshoot would be to arrange for the infusion to commence at a rate which would approximate that required to maintain the T1 at target. This could be accomplished by giving the cumulated error an appropriate starting value

rather than zero. This concept is known as "preloading the integral".

SELECTION OF A VALUE FOR THE PRELOADED INTEGRAL

The manufacturer's recommended dose for atracurium by infusion is 5-10 ug $kg^{-1}min^{-1}$. Since a target of 20% of baseline had been selected it was felt that a slightly lower rate of atracurium infusion would be required to achieve this level of block. The aim, then, was to arrange that following the implementation of the controller the atracurium infusion would start at 4 ug $kg^{-1}min^{-1}$. In order to obtain this flow the preloaded integral must be set at 680.

After the implementation of the controller, the flow of atracurium would then be determined by this equation:

$$\underline{FLOW} = [\underline{K_p} \times \underline{wt} \times \underline{error}] + [\underline{K_i} \times \underline{wt} \times (680 + \underline{\sum error})].$$

This means that for a 70 kg man the flow of atracurium would commence at 33.2 ml hr^{-1}, following implementation of the controller.

This chapter has outlined stages in the development of an algorithm for the automatic control of neuromuscular blockade using atracurium. First three step tests were described from which appropriate actuating parameters for the controller were derived. A simple proportional controller was assessed but found to be unsatisfactory because of a large offset from the target. A PI controller was then tested and shown to be an improvement because it eliminated the steady state error but was still unsuitable as there was a large overshoot of the T1 above the target following commencement of control. The concept of the

preloaded integral was introduced and a suitable value for it calculated.

CHAPTER 6

AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCKADE WITH ATRACURIUM USING A PI ALGORITHM INCORPORATING A PRELOADED INTEGRAL

INTRODUCTION

This study aimed to demonstrate the feasibility of controlling neuromuscular blockade accurately and precisely. Because of its relatively short duration of action and its non-cumulative properties, atracurium was the most suitable relaxant available for automatic control of neuromuscular blockade by infusion.

Proportional and integral gains were derived, the concept of the preloaded integral explained and an appropriate value for this calculated in the previous chapter.

Details of the equipment used and computer programming have been given in earlier chapters.

METHODS

Hospital ethical committee approval was obtained for the study. Thirty-six patients were investigated - all were ASA I or II and none had neuromuscular disease or was taking any medication thought likely to interfere with neuromuscular transmission.

Anaesthetic management of the patients was as outlined for the patients whose relaxant was administered by the proportional and PI algorithms. The automatic controller was switched in when the T1 had recovered to 15% of baseline. This figure was selected arbitrarily to allow for the delay between the start of the infusion and an observable response. Neuromuscular blockade was

maintained by the system until the controller was switched off toward the end of surgery. If the initial atracurium bolus did not cause the T1 to fall to less than 15%, then a further small bolus was given to achieve this. This, in fact, only occurred in one patient (no. 3). The aim was always to have the T1 approach 15% from below.

RESULTS

The details of the patients and their operations are shown in table 3. There were seven males and 29 females. The mean age was 62.5 (SD 10.3) years and the mean weight was 61.8 (SD 13.0) kg.

In no patient did the initial bolus cause the T1 to disappear (the lowest recorded T1 was 2% - in patient nos. 7 and 18). Generally, the T1 fell to around 10%.

It was found that each of the first three patients exhibited an overshoot following commencement of automatic control (with maximum T1s of 28, 23 and 26 respectively) before the T1 began to fall. In an attempt to minimise this problem and the associated potential for patient movement, the value of the preload was increased to the arbitrary figure of 1000 after these three patients. No further changes were made to the program during the study.

Table 4 shows the duration of the controlled period and the mean value achieved for T1 - together with standard deviation (SD) and coefficient of variation (CV) - for that controlled period. The duration of the controlled period was defined in one of two ways depending on whether there was an initial overshoot above target after starting automatic control. If there was, the beginning of the controlled period was taken as the time

Table 3. PI algorithm with preloaded integral - patient data.

Case No.	Sex	Age (a)	Weight (kg)	Operation
1	M	61	80	Carotid Endarterectomy
2	F	39	70	Mastectomy + Axillary Clearance
3	M	72	64	Femoro-popliteal Graft
4	F	60	57	Retinal Detachment
5	F	60	40	Right Hemicolectomy
6	F	68	86	Aortic Bifurcation Graft
7	F	52	75	Carotid Endarterectomy
8	F	58	52	Mastectomy + Axillary Clearance
9	F	69	76	Mastectomy + Axillary Clearance
10	F	50	47	Mastectomy + Axillary Clearance
11	F	60	43	Mastectomy + Axillary Clearance
12	F	59	48	Mastectomy + Axillary Clearance
13	F	73	55	Mastectomy + Axillary Clearance
14	F	77	56	Mastectomy + Axillary Clearance
15	F	78	73	Mastectomy + Axillary Clearance
16	F	66	80	Mastectomy + Axillary Clearance
17	F	67	50	Mastectomy + Axillary Clearance
18	F	68	64	Mastectomy + Axillary Clearance
19	M	46	99	Bilateral Hernia Repair
20	F	73	76	Bilateral Varicose Veins
21	F	77	74	Mastectomy + Axillary Clearance
22	F	61	54	Mastectomy + Axillary Clearance
23	F	66	69	Mastectomy + Axillary Clearance
24	F	76	67	Right Hemicolectomy
25	F	46	64	Mastectomy + Axillary Clearance
26	F	66	60	Mastectomy + Axillary Clearance
27	F	49	60	Mastectomy + Axillary Clearance
28	F	61	55	Cholecystectomy
29	F	59	59	Mastectomy + Axillary Clearance
30	F	67	53	Mastectomy + Axillary Clearance
31	F	45	55	Mastectomy + Axillary Clearance
32	F	66	57	Mastectomy + Axillary Clearance
33	F	46	54	Mastectomy + Axillary Clearance
34	M	69	53	Femoro-femoral Crossover Graft
35	F	75	47	Femoro-popliteal Graft
36	F	65	55	Vitrectomy

Table 4. PI algorithm with preloaded integral - duration, mean T1, standard deviation and coefficient of variation.

Case No.	Duration (min)	Mean T1 (%)	SD	CV
1	34	19.8	0.8	4.0
2	42	19.1	0.9	4.8
3	24	19.3	0.9	4.7
4	34	16.9	1.7	10.1
5	50	18.1	2.6	14.5
6	41	18.0	1.1	6.0
7	77	19.4	2.1	10.8
8	42	20.3	0.7	3.4
9	33	16.3	1.7	10.4
10	21	20.4	1.3	6.5
11	31	21.7	1.2	5.5
12	25	18.9	1.3	6.9
13	24	19.3	0.6	3.1
14	59	20.0	2.0	10.2
15	37	16.8	1.1	6.6
16	47	19.1	2.3	11.9
17	31	20.6	1.5	7.1
18	52	17.9	1.8	10.0
19	74	18.9	3.3	17.7
20	36	16.8	1.6	9.4
21	27	17.2	1.2	6.8
22	33	18.2	1.0	5.2
23	28	17.2	1.5	8.8
24	70	20.1	1.8	8.8
25	23	16.6	1.4	8.2
26	57	19.4	1.2	6.1
27	43	19.4	0.8	4.1
28	54	17.3	1.0	5.9
29	43	18.0	1.5	8.5
30	41	19.3	0.7	3.8
31	49	19.4	0.8	4.2
32	30	19.9	1.0	5.0
33	57	18.3	2.2	11.9
34	64	18.4	1.6	8.5
35	74	18.8	1.2	6.2
36	72	17.4	3.6	20.6

at which the T1 returned to 20% after the overshoot. This pattern is demonstrated in fig. 16A (patient no. 29). If there were no overshoot then the controlled period was taken to begin at the time when the T1 first began to fall after the controller had been implemented. Thirteen patients fell into this second category (nos. 12, 14, 15, 16, 20, 24, 25, 26, 27, 30, 33, 34, & 36) and this pattern is shown in fig. 16B (patient no. 27). This definition of the controlled period was selected as the main interest was in the steady-state period of neuromuscular block. Both figures show that from the beginning of the controlled period until automatic control was terminated, the block was steady and close to the target.

The duration of the controlled period ranged from 21 minutes to 77 minutes with a mean of 43.8 minutes (SD 16.3). In all patients with the exception of no. 6 the controlled period continued until the end of surgery was approaching. In patient no. 6 who was having an aortic bifurcation graft performed the controlled period was terminated when the aortic cross-clamp was applied. It was felt that application of the cross-clamp could potentially lead to alteration in the volume of distribution and possibly produce instability of the control system (see later chapter on patients undergoing cardiopulmonary bypass).

Some comment is required on the degree of overshoot which occurred at the beginning of the controlled period. There was an overshoot in 23 patients. The highest peak T1 obtained in any patient was 29%. In those patients in whom

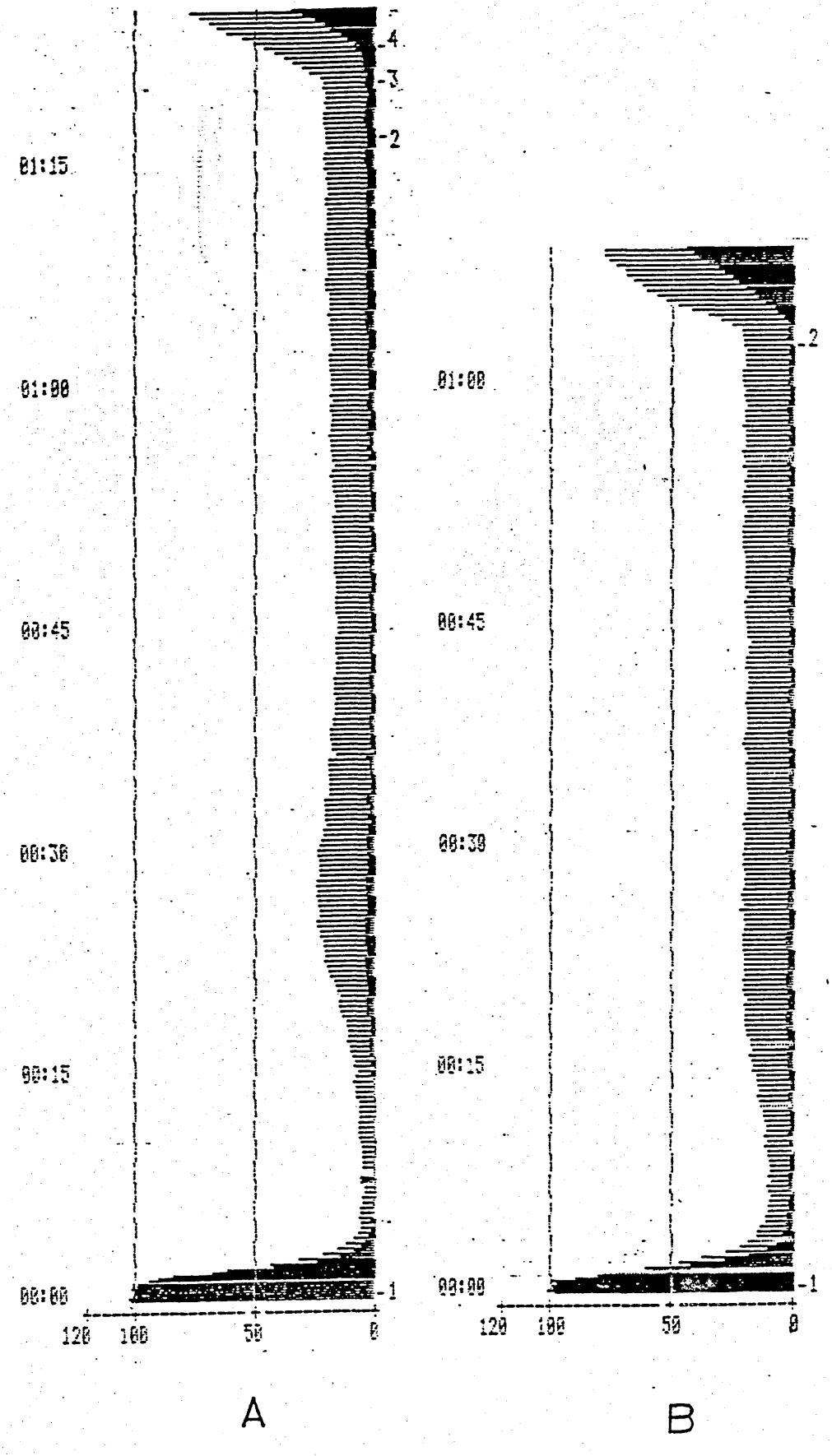


Figure 16. Relaxograph traces obtained using PI control with preloaded integral.
A - with initial overshoot above 20%
B - without overshoot

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there was an overshoot the mean peak value of T1 was 23.7% (SD 2.4).

Using the criteria described above for the definition of the controlled period, the mean time from controller implementation until the beginning of the controlled period was 11 minutes (SD 9.1).

Table 5 gives values for RMSD, PC and dosage. The mean PC was 21.6%. The dosage recorded over the controlled periods ranged from 2.7 ug $kg^{-1}min^{-1}$ to 8.6 ug $kg^{-1}min^{-1}$ with a mean of 5.4 ug $kg^{-1}min^{-1}$ (SD 1.2). Figure 17 is a histogram showing the doses at steady state during the controlled period.

DISCUSSION

Values for mean T1, SD and CV indicate that a remarkably steady level of block was obtained in most of the patients. The RMSD and the PC confirm that the degree of blockade achieved was close to the target in most instances. The closer the mean is to the target the nearer the RMSD will approach the SD. In general, the trend was for the mean to be less than 20%. This can probably be explained by the definition of the controlled period. In those patients in whom there was an initial overshoot, the controlled period began when the T1 returned to 20% - at this point there was still a downward trend in the value of the T1. In the rest of the patients (those in whom there was no overshoot), the controlled period inevitably began at a value less than 20%. As a consequence the initial part of each controlled period started with a series of T1's which were less than the target. Therefore, some time elapsed from the beginning of

Table 5. PI algorithm with preloaded integral - root mean square deviation, point count and dose.

Case No.	RMSD	PC (%)	Dose (ug kg^{-1} min^{-1})
1	0.8	25	6.7
2	1.3	42	4.3
3	1.2	24	4.7
4	3.5	3	4.5
5	3.2	32	6.0
6	2.2	2	5.8
7	2.2	50	5.0
8	0.8	57	6.8
9	4.1	5	4.4
10	1.4	55	6.0
11	2.0	81	7.1
12	1.7	32	5.2
13	0.9	0	8.6
14	2.0	55	5.3
15	3.4	0	6.6
16	2.5	38	4.6
17	1.6	52	5.7
18	2.8	15	4.4
19	3.5	44	4.5
20	3.6	0	4.2
21	3.0	0	6.8
22	2.0	10	5.2
23	2.5	0	5.4
24	1.8	58	5.5
25	3.6	0	4.6
26	1.4	29	5.2
27	1.0	34	4.0
28	2.9	0	5.9
29	2.5	4	8.5
30	1.0	23	5.4
31	1.0	18	6.0
32	1.0	36	5.1
33	2.8	33	4.1
34	2.2	19	4.0
35	1.7	10	5.2
36	4.4	23	2.7

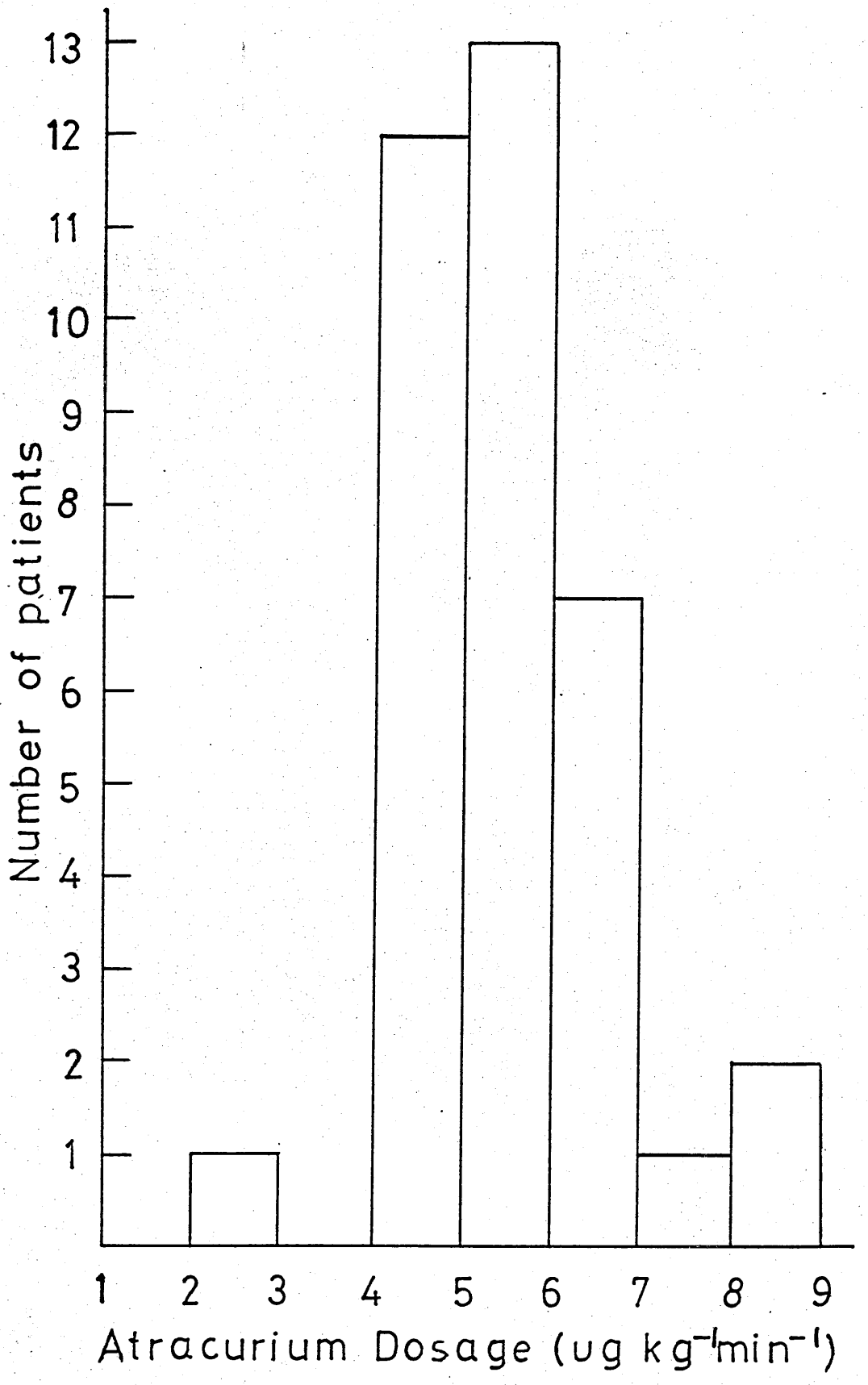

Figure 17. Histogram showing doses of atracurium in steady state period using PI control with preloaded integral.

each controlled period before the T1 returned to 20% and it was the contribution of this initial portion that led to the overall mean T1 being less than the target. It follows that during the latter part of the controlled period the degree of control obtained was superior to that at the beginning and also that, as a general rule, the longer the controlled period the better the degree of control achieved.

In general, the effect of the starting bolus gave a good indication of the subsequent behaviour of the patient. Those patients in whom the bolus caused the greatest falls in T1 tended to be those who required the lowest infusion rates to maintain T1 at target and those on whom the intubating dose had the least effect tended to require a higher infusion rate. This indicates that the effect of a bolus dose gives a reasonable assessment of an individual's sensitivity to atracurium.

The mean dosage recorded is toward the lower end of the range recommended by the manufacturers for atracurium. This is not surprising for three reasons. First, without monitoring, the selected infusion rate should err on the high side because of the inter-patient variability in dose requirements; second, the use of enflurane as in this work will potentiate the effect of any given dose of atracurium; third, a constant infusion maintaining a 20% T1 probably represents the most efficient use of atracurium.

Satisfactory neuromuscular blockade was obtained in all patients. There are a number of reasons why a relatively simple control system of this nature should

work better with atracurium than with other relaxants. Our results show that there is a considerable range in the dosage required to maintain steady state conditions. This has been recorded by other workers (38). These inter-patient variations are, however, less marked than with the other competitive relaxants. D'Hollander et al (97) using vecuronium in 20 ASA I and II patients found that the infusion range to maintain 10% twitch tension was 44-483 ug metre^{-2}body surface area 10 min^{-1}. Also, there is no decrease in the requirement of atracurium in the elderly (30). If this type of control system were used with a relaxant which exhibited greater inter-individual variation there would be a higher chance of instability developing. Those patients who were particularly resistant to the relaxant would demonstrate a marked overshoot on implementation of the controller and in these patients and in those who were especially sensitive there would be a considerable delay before the onset of steady state, provided overt instability did not ensue. It is possible that there are some patients that our system would not control (those at either end of the sensitivity spectrum) but adequate control was obtained for a patient whose requirement was half that of the mean (no. 36) and for another whose requirement was more than 50% greater than the mean (no. 13).

Automatic control has advantages over the standard method of administering relaxants (initial bolus followed by subsequent boluses of approximately one-third the dose) in that it is always possible to exactly quantify the degree of blockade, there are no periods of relative over-

and under-dosage, prompt reversal can be readily achieved if surgery finishes unexpectedly early and the dose of atracurium is minimised.

In summary, a control system has been tested and found capable of successfully controlling neuromuscular blockade in 36 patients. The blockade produced is sufficiently stable to act as a background for further studies into pharmacological and physiological effects on atracurium.

CHAPTER 7

EFFECT OF PROPOFOL ON ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE MAINTAINED BY A FEEDBACK SYSTEM

INTRODUCTION

The work to date on the possible potentiation of muscle relaxants by propofol has been contradictory.

In an in vitro study using the rat phrenic nerve-diaphragm preparation, Fragen et al (18) found that diisopropyl phenol (solubilised in cremophor) potentiated the action of suxamethonium, vecuronium and pancuronium but that cremophor alone antagonised the action of the non-depolarising relaxants. They speculated that if diisopropyl phenol were dissolved in a solvent which did not have an antagonistic action that a greater potentiating effect would be observed with diisopropyl phenol.

Robertson et al (16) studied the effects of diisopropyl phenol on the pharmacodynamics of atracurium in human beings. This paper included four separate investigations - the relevant one being the effect of a bolus of diisopropyl phenol on a steady level of neuromuscular blockade produced by an atracurium or vecuronium infusion. This study is described in some detail below.

Twelve (ASA I or II) patients were studied. Six received atracurium and six vecuronium. Patients were induced with fentanyl 4 ug kg^{-1} and thiopentone 5 mg kg^{-1}. The trachea was intubated shortly after induction without muscle relaxation but with the help of lignocaine spray to the cords. The lungs were ventilated with 67% nitrous

oxide in oxygen and anaesthesia maintained with increments of thiopentone 50 mg, fentanyl 50 ug or droperidol 2.5 mg.

The ulnar nerve was stimulated supramaximally through surface electrodes near the wrist at 0.1 Hz for 0.2 ms. A force displacement transducer measured the response. Patients in the atracurium group received a bolus of 0.1 mg kg^{-1} once a stable twitch height had been obtained followed by an infusion at a rate of 8-12 mg hr^{-1}. A steady 30-60% block was obtained by this method and once this had been maintained for at least 15 minutes, a bolus of 2 mg kg^{-1} diisopropyl phenol was given intravenously over 20 seconds.

The results indicated that there was a decrease of 18.5 $\pm$ 2.4% in twitch height following the bolus. This achieved statistical significance at $P < 0.001$ using Student's t test. This finding corroborated the results of one of the other investigations reported in the paper; that the dose-response curve for atracurium was shifted to the left in patients anaesthetised with diisopropyl phenol compared to similar patients in other studies anaesthetised without diisopropyl phenol. This paper concluded that both vecuronium and atracurium were potentiated by clinical doses of diisopropyl phenol.

No indication was given of the exact level of block achieved before and after the bolus of diisopropyl phenol and there was no indication of how steady this blockade was. No comment was made on the duration of the decrease in twitch height after the diisopropyl phenol bolus. It is worth emphasising that at this time diisopropyl phenol was dissolved in Cremophor EL.

Nightingale et al (17) studied 60 patients in whom anaesthesia was induced with either thiopentone 4 mg kg^{-1} or propofol 2.5 mg kg^{-1} and neuromuscular block achieved with suxamethonium 0.2 mg kg^{-1}, atracurium 0.15 mg kg^{-1} or vecuronium 0.0287 mg kg^{-1}. They found no statistically significant differences in the time to maximum block, maximum depression of T1, maximum depression of TR, time to 50% recovery of T1 between patients who had received thiopentone and atracurium and those who had received propofol and atracurium. They were thus unable to confirm Robertson's results, although they were studying the onset of blockade rather than a steady state phase.

In summary, three papers have been produced on the possible potentiating effect of diisopropyl phenol on atracurium. The first is an in vitro study demonstrating a positive result; the second is a study using anaesthetised patients as their own controls, tending to confirm the result of the first paper. In both these studies diisopropyl phenol was dissolved in cremophor. The third paper (using diisopropyl phenol in its current solvent - a fat emulsion) tends to contradict the earlier findings. Consequently, the situation is not clear.

We have already demonstrated the ability to achieve a very steady level of neuromuscular block by using the PI algorithm described in earlier chapters. This provides an ideal background to assess the effect of propofol on a constant level of block induced by atracurium. By establishing a constant level of neuromuscular block with atracurium (using the feedback control system) and then giving a bolus dose of propofol it should be possible to

determine the effect of the bolus on the level of T1 and the requirements of atracurium. In this way each patient is used as his own control. This method has already been described in the assessment of the effect of diazepam on pancuronium by Asbury et al (80).

METHODS

Ten patients (ASA I or II) were studied. No patient had neurological or muscle disease and none was taking any medication likely to interfere with neuromuscular function. Routine biochemical investigations showed no abnormalities. All patients gave informed consent.

The type of operation required for a study of this sort must fulfill two criteria. First, the operation must be of sufficient length for a stable level of block to be obtained, the bolus of propofol to be given and a new steady state to be achieved and maintained for some time. Second, the surgery should be of a relatively non-invasive type in order to minimise the potential for alterations in atracurium requirement caused by loss of body fluid or decreasing temperature: there should be no significant blood loss and surgery involving open body cavities should be avoided.

The anaesthetic technique was exactly as described for the patients in the PI study with one difference: the appropriate level of enflurane was selected by the anaesthetist in charge of the case. In most instances this was 1% but in some cases, particularly younger patients having vitrectomies, a higher concentration was chosen. Once a percentage of enflurane had been selected which provided satisfactory conditions, no further alteration

was made. Neuromuscular blockade was achieved and maintained using the same PI algorithm (with preloaded integral) as previously. The Relaxograph stimulated the ulnar nerve at the wrist and the flow of atracurium was updated at 20 second intervals. Two infusions were set up: one was dedicated to the atracurium infusion, the other was used for the administration of fluids and other drugs (including the propofol bolus).

When a stable level of neuromuscular block had been achieved for at least 15 minutes the patient was given a bolus of 1 mg kg^{-1} propofol over one minute. Statistical analysis was carried out on the level of neuromuscular block and the atracurium consumption for the 15 minute periods before and after the propofol bolus by using the Wilcoxon signed ranks test.

RESULTS

There were seven male patients and three female. Their mean age was 45.3 years (range 18-75, SD 21.3) and their mean weight was 69.5 kg (range 47-99, SD 18.4). Details are given in table 6.

Representative Relaxograph traces from two patients are shown in figs. 18 & 19. It is immediately obvious that a very steady degree of block was achieved and that there was no striking upset caused by the propofol bolus.

Table 7 gives results for mean T1, standard deviation and coefficient of variation for the 15 minute period before the bolus of propofol, while table 8 gives the corresponding figures for the 15 minutes after the injection of the bolus. The T1 figures are expressed as

Table 6. Propofol study - patient details.

Case No.	Sex	Age (a)	Weight (kg)	Operation
1	M	46	99	Bilateral Recurrent Herniae Repair
2	M	41	82	Vitrectomy
3	M	18	65	Vitrectomy
4	M	69	53	Femoro-femoral Crossover Graft
5	M	20	80	Vitrectomy
6	M	55	95	Vitrectomy
7	F	46	45	Mastectomy + Axillary Clearance
8	M	18	65	Vitrectomy
9	F	75	47	Femoro-popliteal Graft
10	F	65	55	Vitrectomy

Table 7. Mean T1, standard deviation and coefficient of variation before propofol.

No.	Mean T1	SD	CV
1	20.2	0.8	4.1
2	18.2	0.6	3.0
3	18.4	0.6	3.5
4	20.8	0.5	2.5
5	20.5	0.9	4.3
6	19.6	0.5	2.6
7	20.6	0.4	2.0
8	19.5	0.3	1.8
9	19.9	0.4	1.8
10	19.3	0.7	3.5

Table 8. Mean T1, standard deviation and coefficient of variation after propofol.

No.	Mean T1	SD	CV
1	18.5	1.4	7.6
2	19.6	0.7	3.5
3	21.0	0.4	2.0
4	19.5	0.5	2.7
5	19.7	0.4	2.2
6	19.5	0.5	2.3
7	19.6	0.5	2.6
8	19.5	0.4	2.0
9	19.7	0.3	1.7
10	19.5	0.7	3.4

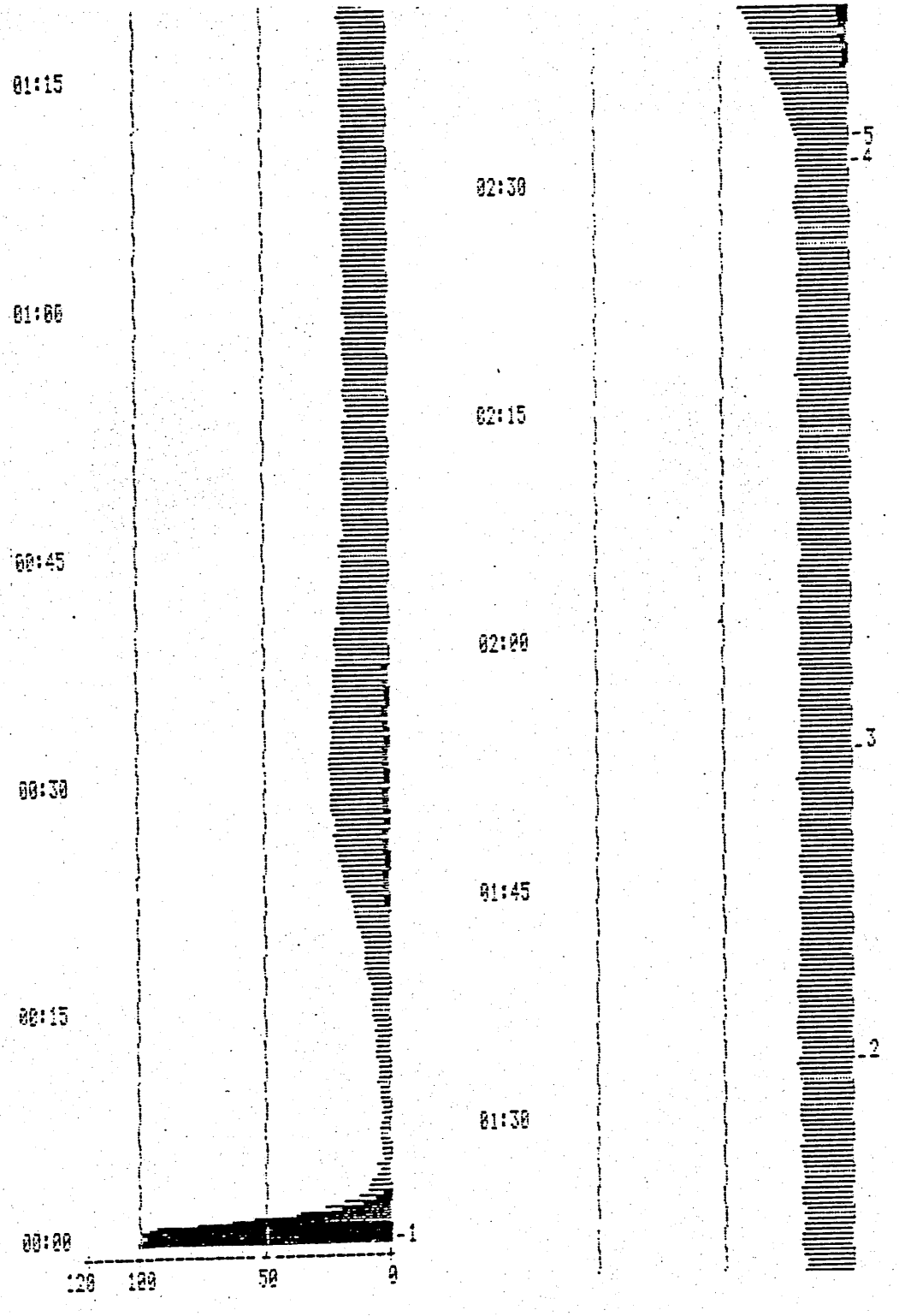

Figure 18. Effect of propofol on steady level of neuromuscular blockade.
Propofol bolus at mark 3.

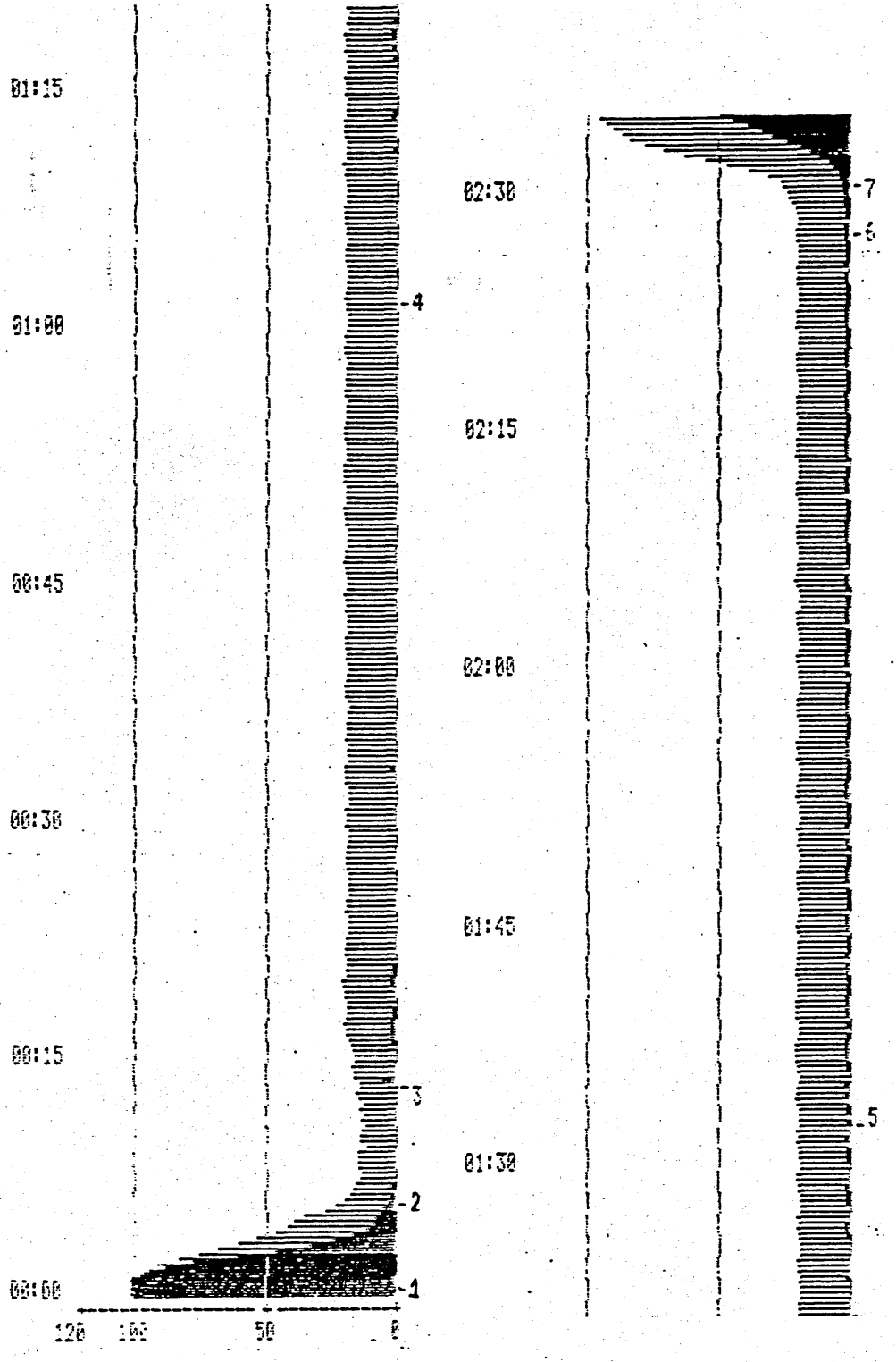

Figure 19. Effect of propofol on steady level of neuromuscular blockade.
Propofol bolus at mark 4.

percentages of the baseline T1, which is taken as 100%. The values for the standard deviations are small, indicating that the feedback control system maintained a steady state. The actual T1 figures indicate that the target was adhered to closely. The average level for the mean T1 before the bolus was 19.7 (SD 0.9) and after the bolus 19.6 (SD 0.6).

Analysis of these data using the Wilcoxon signed ranks test showed that there was no significant difference between the levels of blockade before and after the bolus of atracurium.

Tables 9 & 10 give results for RMSD, PC and dosage of atracurium (in ug $kg^{-1}min^{-1}$) before and after the bolus. In every instance the atracurium requirement after the bolus was less than before. The mean dosage before the bolus was 4.0 ug $kg^{-1}min^{-1}$ (SD 0.9) and after the bolus 3.8 ug $kg^{-1}min^{-1}$ (SD 0.9). Using the Wilcoxon signed rank test there is a statistically significant difference between the dosage before and after the bolus at $P < 0.02$.

DISCUSSION

With the stable pharmacological background produced by a feedback control system, an environment is produced which provides an opportunity to detect the presence of any interaction between propofol and atracurium in circumstances which are more precisely controlled than any hitherto described. The system assumes that the consumption of atracurium remains constant after steady state has been achieved (atracurium's non-cumulative properties should ensure that this is the case) and that the level of block will also remain constant unless there

Table 9. Root mean square deviation, point count and atracurium dose (ug $kg^{-1}min^{-1}$) before propofol.

No.	RMSD	PC	Dose
1	0.8	60	4.9
2	1.9	0	3.5
3	1.8	0	2.8
4	0.9	80	4.0
5	1.0	74	4.0
6	0.6	7	4.7
7	0.7	93	4.1
8	0.6	0	4.9
9	0.4	13	4.9
10	1.0	11	2.5

Table 10. Root mean square deviation, point count and atracurium dose (ug $kg^{-1}min^{-1}$) after propofol.

No.	RMSD	PC	Dose
1	2.1	11	4.5
2	0.8	39	3.4
3	1.1	97	2.5
4	0.7	7	3.8
5	0.5	28	3.8
6	0.7	0	4.6
7	0.7	34	3.9
8	0.6	2	4.7
9	0.5	0	4.8
10	0.8	9	2.3

is some perturbation (this is why cases which caused minimal physiological upset were selected).

If there were a potentiating effect, one would expect a reduction in the T1 initially followed by a gradual return toward target. There would be a corresponding diminution in the atracurium infusion rate.

It is interesting that there should be no alteration in the T1 but a decrease in the infusion rate. There are a number of possible explanations for this.

First, it may be that the change in infusion rate represents a genuine potentiating effect of propofol on atracurium. The absolute values of the changes in infusion rates suggest that if there is a real effect then it is unlikely to be of clinical significance.

Second, as the majority of these procedures were long it is possible that there was a gradual diminution in the patient's temperature over the course of the operation. This would prolong the action of the atracurium present (by inhibiting the Hofmann elimination pathway) and consequently less atracurium would be required to maintain the same degree of block.

Third, there is a possibility that drift of the Relaxograph electrodes occurred during the operation. This phenomenon has been described elsewhere (57). Carter et al described five patients who were studied in order to assess the stability of the Relaxograph. All were young and fit and required tracheal intubation for dental surgery. The machine was calibrated and the value of the supramaximal stimulus noted after induction of anaesthesia but before the administration of suxamethonium. At the end

of the procedures (which varied from 25-90 minutes), the instrument was recalibrated and the second supramaximal stimulus noted. In all cases the value of the second supramaximal stimulus was identical to that of the first. Despite this the authors still believe that instability of the Relaxograph may be a potential problem. The reasons for this are not clear.

The following are advanced as possible explanations by Carter. Movement of the forearm or hand may alter the position of recording and stimulating electrodes relative to each other. The effects of drugs other than neuromuscular blockers may have a role to play. One has to consider here the potentiating effect of volatile agents on competitive relaxants - remembering that the patients described in Carter's study did not receive any competitive blockers. The effects of changing pH, blood gas concentrations and electrolytes have not yet been clarified. Another factor which may be important is the alteration in electrode impedance with time and temperature. The temperature effect is likely to be most pronounced in patients undergoing major surgery involving the opening of body cavities with associated major heat loss and poor peripheral perfusion.

Analysis of the computer printouts associated with each of our cases shows that over the time of the controlled period there was a gradual decline in the infusion rate required to maintain the target. If, for example, the calculated infusion rates for patient no. 8 are analysed it will be seen that the infusion rate at the beginning of the controlled period (as previously defined)

was approximately 42 ml hr^{-1} while at the end the rate was approximately 32 ml hr^{-1}. This general pattern is repeated in all of these propofol cases. In none of the cases is there a marked alteration in the infusion rate at the time of the propofol bolus. This fact suggests that the alteration in atracurium requirements after the propofol bolus is part of a general decrease in requirements rather than specifically related to the propofol.

Consequently, it seems that the explanation for the decrease in infusion rate lies with either a gradual fall in the patient's temperature or with electrode drift.

CONCLUSION

The results show that there is no significant effect of propofol on a steady state level of neuromuscular blockade achieved with atracurium using a feedback control system. The atracurium infusion rate required to maintain blockade was statistically significantly less following a bolus dose of propofol but the reasons for this seem to lie with causes other than the potentiation of atracurium by propofol.

It is concluded that propofol has no clinically relevant potentiating effect on atracurium.

CHAPTER 8

AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCKADE IN PATIENTS REQUIRING CARDIOPULMONARY BYPASS

INTRODUCTION

Considerable confusion has existed for some time concerning the action of hypothermic cardiopulmonary bypass (CPB) on neuromuscular transmission per se and when this is modified by different muscle relaxants. This chapter begins with a review of work relating to the effects of CPB on muscle relaxation and its monitoring.

Park and Macnamara (98) studied 16 patients undergoing surgery requiring CPB and divided them into four groups of four depending on which of two relaxants (d-tubocurarine or pancuronium) they received and whether or not they were cooled. Anaesthesia was maintained with nitrous oxide, oxygen and morphine. Neuromuscular transmission was monitored by means of a Grass force-displacement transducer. After intubation supplementary doses of relaxant were given to maintain twitch height between 5-25% of control. No further relaxant was given from a point 30 minutes before the start of CPB.

In both hypothermic and non-hypothermic groups there was an initial rapid increase in twitch height at the beginning of bypass. In the hypothermic group the twitch height then began to decline steadily before slowly increasing - the warming phase resulting in a faster recovery of twitch height. The normothermic groups showed continued slow recovery after the initial rapid recovery. There was no obvious difference in the response patterns obtained with different relaxants. The initial rapid recovery in both hypothermic and normothermic groups at

the start of CPB was attributed to an initial rapid fall in plasma relaxant concentration due to sudden dilution with prime solution. No satisfactory explanation was produced for the enhancement of blockade during the hypothermic phase.

D'Hollander et al (99) looked at ten patients to determine the effects of hypothermic CPB on the neuromuscular block produced by pancuronium. They measured infusion rates, plasma concentration of pancuronium and adductor pollicis temperature every 15 minutes. An opiate-based anaesthetic technique was used. Neuromuscular function was monitored with a Grass 88 nerve stimulator and a Statham force transducer. After stable baseline values were obtained pancuronium 0.07 mg kg^{-1} was administered and the trachea intubated. From this point the twitch height was maintained at around 10% of its initial value by manually adjusting the infusion rate of a syringe pump loaded with pancuronium in saline. They found that pancuronium requirements during the hypothermic phase were about 60% less than during the normothermic phase, although there was an increase in pancuronium requirement at the commencement of bypass.

The increased requirements at the start of CPB were again attributed to the substantial increase in circulating volume and consequent increase in volume of distribution. D'Hollander also pointed out that the fall in plasma protein concentration resulting from haemodilution would increase the proportion of free pancuronium. This would tend to limit the increase in pancuronium requirements. They concluded that from the

practical point of view pancuronium requirements increased at two specific moments: at the start of CPB and during rewarming.

D'Hollander et al also analysed the urinary excretion of pancuronium in five of the ten patients over five separate periods (prebypass, cooling, hypothermia, rewarming and postbypass). No significant differences were found between any of the groups. This information excluded compromised renal function during hypothermia as a cause of the increased potency of pancuronium.

The first of two papers which have studied the use of atracurium during hypothermic cardiopulmonary bypass was by Flynn, Hughes and Walton (100). They studied 12 patients, monitoring neuromuscular function with a force transducer. An initial bolus of 0.6 mg kg^{-1} followed by an infusion of 6.6 ug $kg^{-1}min^{-1}$ was sufficient to maintain 90-95% block before bypass. The same degree of blockade was maintained with an infusion of approximately half this rate during the hypothermic phase. The commencement of CPB had no effect on the degree of block. It is interesting that two patients are described who started to breathe during the hypothermic period despite the absence of response to ToF or tetanic stimulation (this may have been the result of the different effects of CPB on force transducer monitoring compared to electromyographic, see below). They also comment that the infusion rate required to maintain the same twitch height was significantly lower after bypass than before. They ascribed the potentiation of atracurium during hypothermia to a reduced rate of Hof mann elimination. The pattern is almost certainly more

complex than this, however. If the above were the sole explanation for the potentiation of neuromuscular blockade during hypothermic CPB, why should other relaxants behave similarly?

Buzello and co-workers have produced three papers relating to this topic in recent years. In the first, 20 patients undergoing CPB were studied (101). They received a nitrous oxide-narcotic anaesthetic and were randomly assigned to receive either pancuronium or vecuronium. Neuromuscular transmission was monitored with the evoked EMG at the right wrist and changes in this were related to nasopharyngeal temperature. This was the first of the papers described in which electromyography was used as the method of monitoring. Initial doses of 0.075 mg kg^{-1} of both drugs were given followed by supplementary boluses of 0.015 mg kg^{-1} whenever the size of the EMG action potential had recovered to 25% of baseline.

They concluded that hypothermic CPB increased the duration of action of pancuronium and vecuronium and that during CPB vecuronium was no longer a shorter acting relaxant than pancuronium. The prolonged action of both drugs was partially reversed by rewarming and there was no significant difference from prebypass requirements during normothermic perfusion or in the post-bypass phase.

The explanation for the increased duration of block under hypothermic conditions is not clear. Buzello concluded that hypothermia increased the effect of muscle relaxants at the level of the neuromuscular junction rather than at the level of drug disposition or degradation.

In an attempt to clarify the effect of hypothermic cardiopulmonary bypass on neuromuscular transmission, Buzello et al (102) devised a project whereby neuromuscular transmission was simultaneously monitored by EMG and twitch tension, without muscle relaxants, in patients undergoing open heart surgery. Induced changes were related to nasopharyngeal temperature. Ten patients were studied and received a nitrous oxide-narcotic anaesthetic. Twitch tension was shown to be moderately reduced during cooling and to overshoot above baseline on rewarming: EMG potentials, in contrast, increased on cooling and returned to baseline after rewarming.

This work agrees with that of Ricker et al (103) who showed that local cooling of the forearm in conscious volunteers depressed the mechanical twitch response while augmenting the potential of the simultaneously recorded compound EMG. This implies that the effects on both the EMG and the twitch tension are a result of hypothermia rather than other factors present during CPB (e.g. haemodilution, electrolyte imbalance, altered pharmacokinetics or anaesthesia).

Possible explanations for increased EMG activity during hypothermia include facilitated transmitter release and increased sensitivity of the post-junctional membrane to acetylcholine. The depression of twitch tension is probably caused by hypothermia-related contractile failure. In essence, neuromuscular function is facilitated at the myoneural junction but inhibited at the level of mechanical contractility in the presence of hypothermia and these effects are due to altered muscle temperature.

Modifications of partial neuromuscular block during hypothermic bypass are thought to be the result of muscle relaxants increasing or decreasing the effect of hypothermia on normal neuromuscular transmission.

This is an important piece of work which makes it clear that comparisons between different relaxants during CPB are invalid unless the same method of monitoring is used.

Denny and Kneeshaw (104) compared 25 patients having coronary artery bypass surgery using atracurium and vecuronium. Compound EMG was monitored using a Datex Relaxograph. Initial boluses of either relaxant brought the T1 down to 5% of control and this level was maintained by adjusting the rate of an infusion of the relaxant. They found that 35% less atracurium and 71% less vecuronium were required to maintain the same degree of block during hypothermic CPB. In both cases these results were highly statistically significant.

They explained their results on the basis of work done by Thornton et al (105) in which a reduction in twitch tension was found in the legs of dogs cooled by blood taken from the carotid artery via a heat exchanger. This reduction was greater when indirect stimulation of the muscle was used compared to direct. This suggests that the diminution in twitch tension may have a presynaptic as well as a post-synaptic component and is attributed to partial failure of acetylcholine release (exactly the opposite conclusion to Buzello in the previous paper).

The most recent contribution in this field is again from Professor Buzello (106). He described 40 patients,

undergoing open heart surgery, who were randomised to four groups receiving one of four relaxants - alcuronium, d-tubocurarine, pancuronium and vecuronium. Patients were anaesthetised with flunitrazepam, fentanyl and nitrous oxide and the trachea was intubated without muscle relaxation. The EMG and the evoked twitch tension were monitored simultaneously. Paralysis was provided by a bolus of relaxant followed by an infusion - the dosages were selected in an attempt to achieve a steady block of 30-60% in the prebypass phase.

In patients receiving alcuronium, d-tubocurarine and pancuronium hypothermic CPB attenuated neuromuscular blockade while vecuronium blockade was enhanced, as measured by the EMG. The trend of the twitch tension results was the same but the changes were less marked. It is noteworthy that the results for pancuronium and EMG monitoring are at variance with Buzello's earlier work.

Buzello suggested that the facilitating effect of hypothermia on EMG voltage and its inhibiting effect on twitch tension could be augmented or depressed by individual relaxants. He postulated altered local diffusion and receptor affinity as a function of temperature as a possible explanation.

The observed effects of hypothermic CPB on neuromuscular function depend firstly on the method of monitoring employed. Hypothermic CPB has been shown to potentiate neuromuscular blockade induced by atracurium or vecuronium in every study in which they have been used. In some cases there was a transient attenuation of block at the start of CPB (generally attributed to the associated

increase in volume of distribution). The results for the other relaxants are less clear. For example, a pancuronium-induced block in patients undergoing hypothermic CPB - which was studied in four publications - was found to be augmented in three papers (98, 99, 101) and diminished in one (106).

Automatic control of neuromuscular blockade has not previously been described in patients having open heart surgery and the prospect was intriguing for a number of reasons. The commencement of CPB (with its associated haemodilution) and hypothermia subject a control system to the most challenging physiological upset which is available in normal clinical practice. If the system were inadequately designed then it could oscillate. If the system were able to achieve steady levels of blockade at differing points of the procedure then it would be possible to compare the atracurium requirement at different stages of the operation. It was hoped that it would be possible to separate the effects of sudden haemodilution and hypothermia on the level of neuromuscular block at the start of CPB.

METHODS

Eleven patients were studied. All were having coronary artery bypass surgery. The same consultant anaesthetist was in charge of all cases. Because one of the aims was to subject the control system to maximal stress, no modification was made to the anaesthetic technique. In particular no restriction was placed on the use of volatile agents.

Premedication was with temazepam 40 mg and ranitidine 150 mg two hours before surgery. In the anaesthetic room, under local anaesthetic, a 14 gauge cannula was inserted into a peripheral vein in the right forearm and a 20 gauge cannula was inserted into the left radial artery. Relaxograph electrodes were attached to the left wrist and secured as described previously. The patient was then transferred to theatre where electrocardiographic and direct blood pressure monitoring were established. The left wrist was tightly wrapped in gamgee and immobilised at the patient's side with a series of J-boards.

Anaesthesia was induced with fentanyl (0.5-1.0 mg) and midazolam (5-10 mg). After this baseline values were obtained with the Relaxograph. The patient was then given a bolus of 0.25 mg kg^{-1} atracurium. Ventilation was supported and then controlled as the T1 fell and when this had reached 25%, the trachea was intubated and automatic pulmonary ventilation commenced. Additional boluses of atracurium were given to maintain the T1 at less than 15% until the right internal jugular vein was cannulated (and, in some cases, the pulmonary artery). At this point the T1 was allowed to recover to 15% and the atracurium infusion started under the control of the PI algorithm with preloaded integral (as described earlier). Neuromuscular blockade remained under automatic control until the end of the operation. Anaesthesia was maintained with 50% nitrous oxide in oxygen, fentanyl and midazolam supplemented by enflurane if required. The patients were ventilated with

100% oxygen. Vasodilators and inotropes were used as necessary. Enflurane was not used in the postbypass phase.

Monitoring included ECG, direct blood pressure, central venous pressure (and sometimes pulmonary artery pressure), urinary output, temperature (naso-pharyngeal and peripheral), arterial blood gases, serum electrolytes and activated clotting time.

RESULTS

The mean age of the patients studied was 53.8 years (range 30-66, SD 12.0) and the mean weight 75.2 kg (range 46-99, SD 14.8). Table 11 summarises the patient data.

A typical tracing from the study is shown in fig. 20. A steady level of block is achieved at the target relatively quickly. The surgical incision was at mark 4 and at this point enflurane was started. Enflurane was discontinued at mark 7 and CPB commenced at mark 8. Here the patient's naso-pharyngeal temperature was 34.0^{o}C. The succeeding marks indicate falling temperature until the minimum was reached at mark 15 - 26.0^{o}C. At mark 16, the value of the proportional and integral terms was such that the calculated infusion rate was zero ml hr^{-1}. Although the infusion rate now defaulted to 0.1 ml hr^{-1}, the integral continued to fall with each successive measurement of T1 (because all the values were less than 20). There is a potential problem here. If the integral assumes a significant negative value then the infusion rate will remain at 0.1 ml hr^{-1} even though the T1 exceeds the target. Accordingly, the system was restarted when the T1 had once again recovered to 15%. This occurred at

Table 11. Cardiopulmonary bypass study - patient details.

Case No.	Sex	Age	Weight
1	M	66	73
2	M	42	95
3	F	67	64
4	M	64	80
5	M	47	83
6	F	56	64
7	M	46	99
8	M	50	76
9	M	60	77
10	M	30	70
11	F	65	46

Table 12. Cardiopulmonary bypass study - results.

	No.	Mean T1	SD	Dose	RMSD	PC
Pre	1	19.1	2.3	4.1	2.5	26
Post		20.1	0.6	4.0	0.7	32
Pre	2	22.1	1.0	5.7	2.4	100
Post		17.7	2.5	4.8	3.3	21
Pre	3	19.6	1.0	5.3	1.0	25
Post		19.2	3.9	7.2	3.9	34
Pre	4	18.3	1.9	3.1	2.6	38
Post		24.1	2.0	5.0	4.6	100
Pre	5	18.5	4.3	2.8	4.5	43
Post		19.4	1.0	3.7	1.2	16
Pre	6	24.0	1.4	6.1	4.2	100
Post		24.4	1.5	6.6	4.6	100
Pre	7	21.1	1.2	5.3	1.6	79
Post		16.3	2.0	4.0	4.2	0
Pre	8	17.6	2.3	2.9	3.3	21
Post		19.9	2.2	2.6	2.2	54
Pre	9	20.6	1.1	5.4	1.3	63
Post		17.7	0.9	5.2	2.5	2
Pre	10	23.4	2.0	8.0	4.0	100
Post		20.9	0.8	2.7	1.2	86
Pre	11	19.6	1.1	6.0	1.1	34
Post		19.8	1.8	5.9	2.7	36

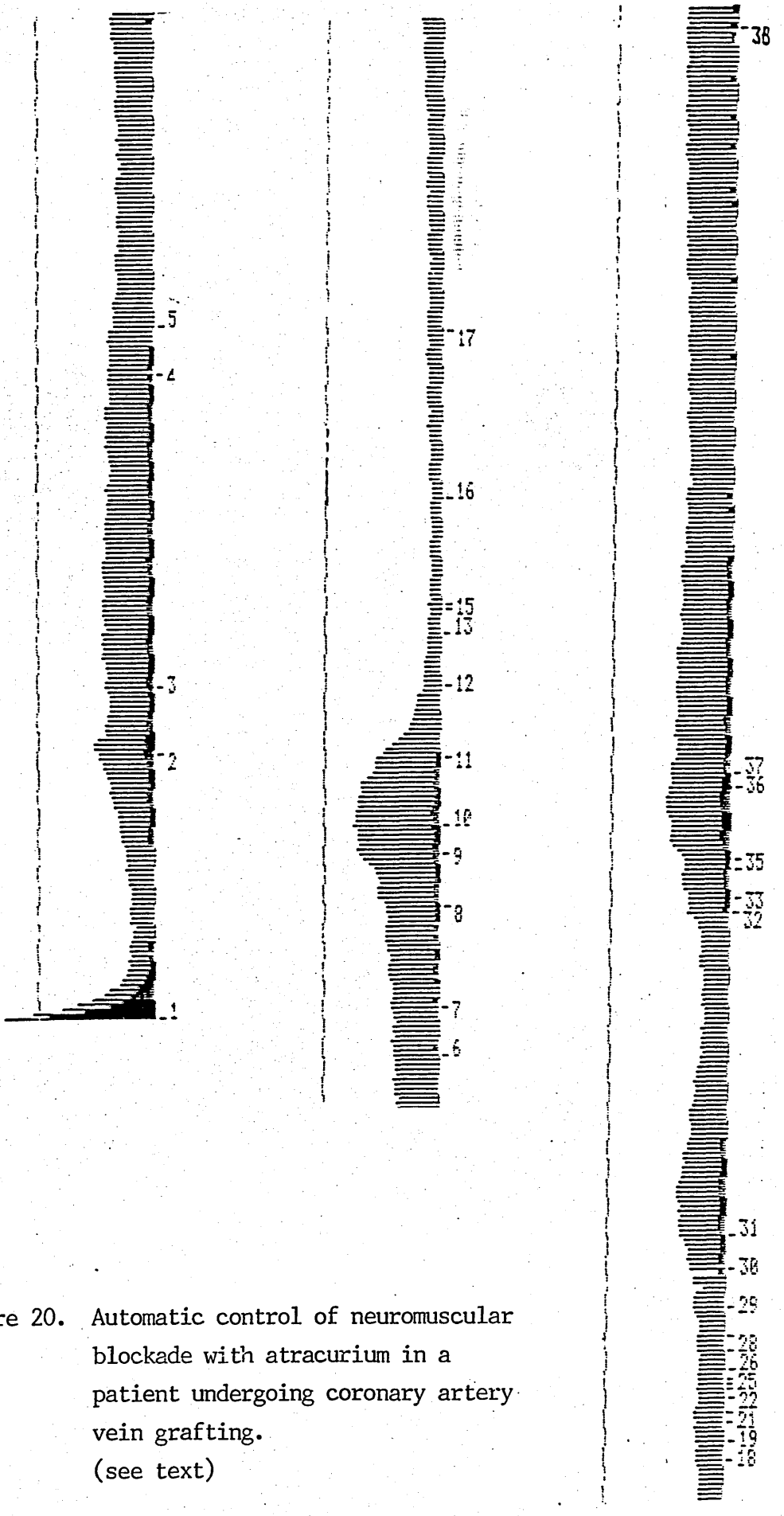

Figure 20. Automatic control of neuromuscular blockade with atracurium in a patient undergoing coronary artery vein grafting.
(see text)

mark 30. Rewarming commenced at mark 18 and at mark 29, the temperature was 36°C. In this case, therefore, rewarming was complete before the system was restarted. CPB was discontinued at mark 35.

Operations involving hypothermic CPB can be divided into three separate phases: prebypass, CPB (which has four subphases - cooling, hypothermic CPB, rewarming, normothermic CPB) and postbypass. The controller was able to achieve steady state at target during only the prebypass and postbypass phases. The cooling, rewarming and normothermic bypass periods proved too short (and probably too dynamic) for steady state to be achieved. Consequently statistical comparisons can be made only between the first and last phases. Table 12 provides information from steady state periods, pre- and postbypass.

The periods over which these figures are calculated relate to the 20 minute periods immediately before CPB commenced and, in the post-bypass phase, immediately before the control system was discontinued. The mean T1 for the prebypass period was 20.3 (SD 2.1) and for the postbypass period 20.0 (SD 2.5). Individual values for SD, RMSD and PC indicate that good control was achieved in all patients. Analysis of the pre and postbypass T1s by Wilcoxon's signed ranks test showed no significant difference between the two groups.

The mean dosage at steady state was 5.0 ug kg^{-1} min^{-1} (SD 1.6) in the prebypass period and 4.7 ug kg^{-1} min^{-1} (SD 1.5) in the postbypass. Comparison of the dosages using Wilcoxon's rank signed test again showed no

statistically significant difference between the pre and postbypass data.

Of the 11 patients studied, seven showed a marked increase in T1 immediately following the commencement of CPB, associated with an increase in the infusion rate of atracurium, as illustrated in fig. 20. In these patients the highest T1 recorded during this phase was 39% and the mean of the peaks recorded was 32%. In the other four patients the pattern was as shown in fig. 21, with minimal rise in T1 at the start of CPB, which is at mark 10.

All patients showed a marked reduction in T1 and atracurium input during the cooling and hypothermic periods. With the exception of patient 9, the controller stopped the infusion in all patients during the hypothermic period (and in patient 9, who had a relatively short bypass, the infusion rate was reduced to 2 ml hr^{-1}). During the rewarming period there was an increase in atracurium requirements and the T1 rose above 20%. It is not possible to quantify this rise in a meaningful way because it was not preceded by a constant level of block.

There are two other minor but interesting points. Fig. 20 demonstrates the first. At mark 30 the patient was directly defibrillated and the subsequent value for T1 was zero. The second point is illustrated in fig. 21. At mark 24 the patient was given a bolus of calcium chloride 10 mmols. This resulted in a marked attenuation of the block. Both these patterns were observed in other cases.

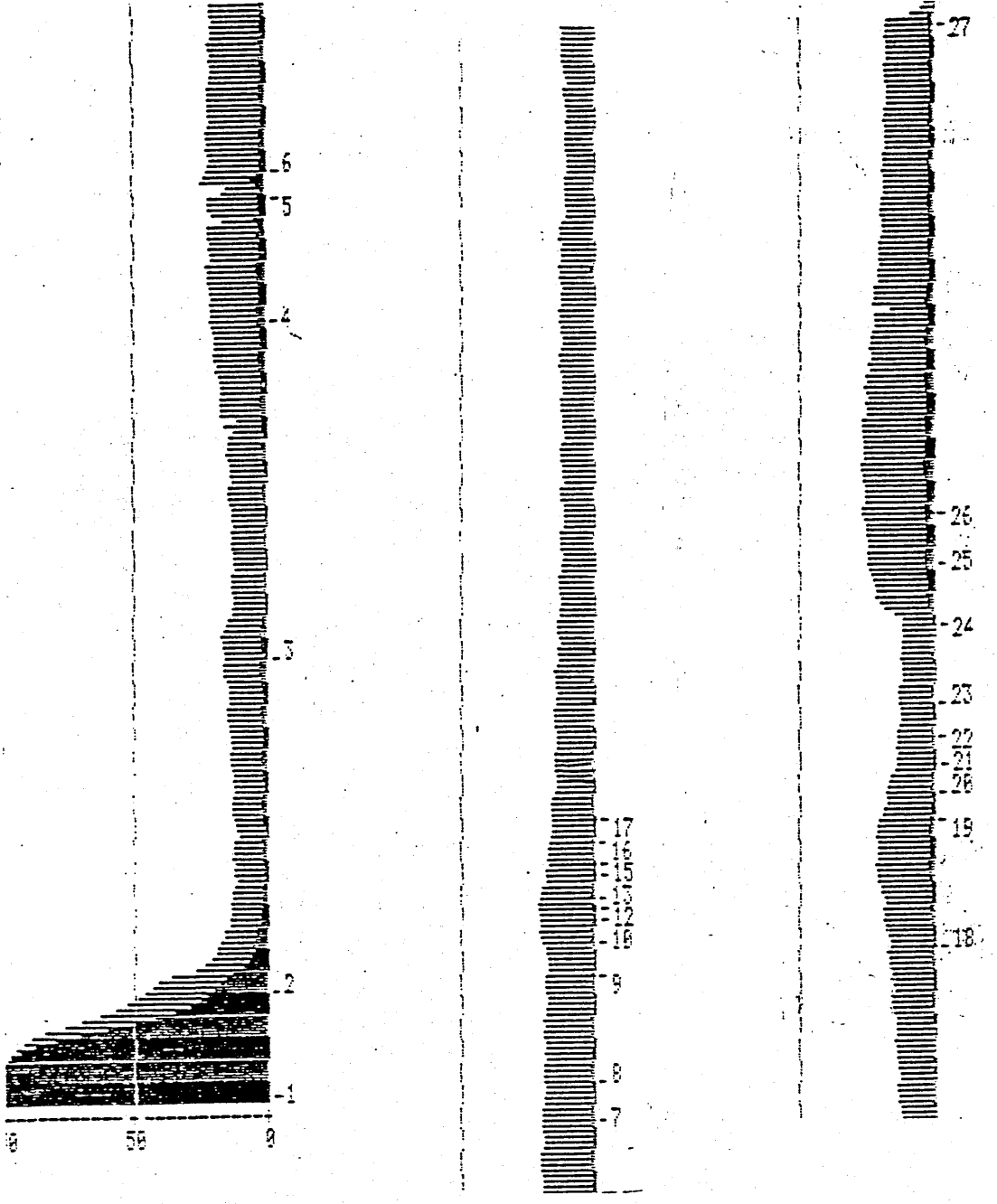

Figure 21. Automatic control of neuromuscular blockade with atracurium in a patient undergoing coronary artery surgery.
(see text)

DISCUSSION

The discussion is divided into two parts: commentary on the results of the present study in comparison with previous work and assessment of the control system.

In contrast to the work reported by Flynn et al (100) and Denny and Kneeshaw (104), we found that there was a marked attenuation of blockade (as denoted by an increase in T1 at the start of CPB) in seven of 11 patients. The explanation for this phenomenon is almost certainly that given by Park and Macnamara (98), i.e. at this point there is a substantial increase in the volume of distribution of atracurium - this leads to a fall in plasma concentration and therefore decreased activity at the receptor site. In three of the four patients in whom this initial rise did not occur it is noticeable that the onset of hypothermia was very rapid - the effect of cold in potentiating the block was almost simultaneous with the effect of haemodilution in attenuating it (cf. figs. 20 and 21, where the marks immediately succeeding the onset of CPB indicate falling temperature in 1^{o}C steps).

Dosage requirements for atracurium to maintain the same level of block are unchanged in the postbypass phase in comparison with the prebypass. This conclusion differs from that reported by Flynn et al (100) who found that infusion rates to maintain the same degree of block were significantly less in the postbypass phase. Flynn's work, however, was carried out using a force transducer as the monitor of neuromuscular function and therefore direct comparisons are not possible. Buzello (106) has pointed out that (in the case of alcuronium, at least) the

correlation between EMG and twitch tension is irreversibly lost during hypothermia. It may be that the same argument applies to atracurium. It seems that electromyography provides the best monitor for patients requiring hypothermic CPB: Buzello found in his study without muscle relaxants (102) that following the bypass period the EMG returned to prebypass levels whereas the twitch tension overshot the baseline level.

The present study does not shed much further light on the mechanism of the attenuation of neuromuscular blockade during the hypothermic phase. Though the theory that hypothermia reduces atracurium elimination by inhibiting the Hoffman elimination pathway is attractive, it seems unlikely that this is the whole explanation. Buzello's contention that the facilitation of the EMG during hypothermia can be enhanced or inhibited by specific muscle relaxants (inhibition in the case of atracurium) is the most plausible explanation offered to date.

The effect of defibrillation on the EMG can easily be explained on the basis of electrical interference. The effect of calcium is more subtle but equally readily explained. An increase in the concentration of calcium around the neuromuscular junction promotes the release of acetylcholine from the nerve ending and this extra acetylcholine is able to compete more effectively with the relaxant for the receptor sites on the motor end-plate (2), thus decreasing block.

As mentioned in the introduction, cardiac cases were chosen as those which would provide the most stringent test for an automatic control system using atracurium,

combining the massive physiological trespasses of haemodilution and hypothermia with large-scale pharmacological intervention.

The controller performed reasonably well. In all cases a satisfactory degree of block was achieved before the institution of CPB, despite the potentiating effect of enflurane which was evident in some cases (see fig. 20).

There was a loss of control in seven of the 11 cases at the start of CPB but in all patients the combined effect of the controller and the onset of hypothermia prevented the T1 from rising above 40%. It would be interesting to run the system on a patient requiring normothermic CPB in order to separate the effect of haemodilution from that of hypothermia. The alteration in the circulating volume is so rapid and so large (an addition of two litres in less than one minute) that it is unlikely that any control system (even of the adaptive type) would not be substantially affected by it.

There was a marked diminution in atracurium requirements and in the level of T1 during the hypothermic phase in each patient. The controller responded in all cases but one by stopping the infusion. It was necessary to restart the control system again when the T1 had recovered to 15%, either during the rewarming phase or during the hypothermic phase if this proved to be especially long. As explained in the results section this was to prevent the accumulation of a negative integral which would act in such a way that the infusion would not recommence until the T1 had risen well above the target. Alterations in the program such that the infusion was

halted each time the T1 fell below 15% and the control algorithm commenced afresh when recovery to above this value occurred would be relatively simple and would eliminate this problem.

A self-tuning system would reduce the infusion rate of atracurium more promptly during the hypothermic period but since the current system terminated the flow of relaxant relatively quickly anyway, this would be unlikely to confer any benefits in terms of patient safety.

The controller dealt satisfactorily with the changes occurring during rewarming and at the end of CPB. In some cases there was a slight attenuation of block as bypass was terminated (fig. 20, mark 35) but this was not a consistent feature. The explanation for this is not clear: a potentiation of block might be expected because there is a relatively rapid reduction in the volume of distribution of atracurium at the end of CPB which will precede any associated decrease in infusion rate. One possible explanation is that the termination of bypass is often associated with hypotension which may be treated by rapid infusion of fluid - such an infusion would cause a decrease in the plasma concentration of atracurium and therefore a reduction in neuromuscular block.

During the postbypass period the automatic control system was able to achieve a constant level of blockade which was very close to the target.

In summary, this work has demonstrated that a relatively simple feedback system is capable of achieving satisfactory control of neuromuscular blockade even in the complex physiological and pharmacological environment

provided by a patient undergoing coronary artery bypass grafting. It has also established that there is an attenuation of blockade at the start of CPB and that there is no important difference in atracurium requirements between the pre and postbypass phases.

CONCLUSIONS

The main conclusions to be drawn from the work of this thesis are that a precise and accurate degree of blockade can be obtained satisfactorily using a relatively simple PI system and that this steady state provides a suitable background for the study of physiological and pharmacological effects on atracurium.

In almost all cases a T1 of 20% of the baseline proved satisfactory. In one case the operator complained that the abdominal muscles were "tight" on closure. It may be that aiming for a target T1 of 15% in future studies would eliminate this problem. The 20% target was chosen because it was felt that this would provide satisfactory blockade and because the working point would be within the linear part of the dose-response curve for atracurium. Selecting a lower target (e.g. 10%) would invite the problem of the working point moving outwith the linear part of the dose-response curve. Further, a slight overdose at this level of T1 would push the system into saturation and render the PI equation inoperable.

The effects of two anaesthetic agents on atracurium are seen clearly in this project.

Propofol was specifically studied and it was concluded that it had no clinically significant effect on atracurium. It has been suggested that a dose of 1 mg kg^{-1} might not be sufficient to display any potentiation and that we should have used a larger bolus. The dose used was, however, sufficient to cause a transient fall in blood pressure of 10-15 mm Hg in all cases. We were consequently wary of using a larger bolus which would

approach a full induction dose in a patient who was already adequately anaesthetised.

We did not specifically study the potentiating effect of enflurane but its effects were evident in a number of cases. The pattern can be seen in fig. 20 where the commencement of enflurane coincides with a diminution of T1 (see chapter 8). In some of the propofol cases (chapter 7) in which a concentration of enflurane greater than 1% was used, an attenuation of the block was noted as the enflurane concentration was reduced toward the end of surgery.

The cases involving CPB demonstrated that the controller was capable of maintaining satisfactory neuromuscular blockade in that challenging environment. The effect of haemodilution in attenuating the block was evident in seven of the cases and in all but one the atracurium requirement was sufficiently low during the hypothermic period that the infusion was terminated. It was generally possible to separate the effects of haemodilution and hypothermia. It was concluded that the atracurium requirements in the postbypass phase were no different from the prebypass phase.

The advantages of an automatic control system are that, with the constant block produced, the potential for reversal is always known, there are no periods of relative under or over dosage, the dosage of relaxant is minimised and the background produced can act as the basis for further research.

Possible future work includes the development of a more sophisticated controller with a self-tuning facility.

Clinical work has already commenced in the Western Infirmary, Glasgow in this field.

Another area of anaesthetic interest which could be explored with the system developed and tested in this thesis is the effect of varying levels of end-tidal carbon dioxide. It should also be possible to quantify the degree of potentiation produced by the different volatile agents at varying concentrations on atracurium requirements.

Finally, although the degree of control obtained using atracurium was satisfactory, it is likely that employing a shorter acting agent would achieve steady block more rapidly. It is also likely that such a system would react more rapidly to any external influences. The advent of new short-acting competitive relaxants is keenly awaited.

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APPENDIX 1

PROGRAM FOR AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCKADE

WITH PI ALGORITHM INCORPORATING PRELOADED INTEGRAL

```
10 REM DATE 6/5/87
20 REM PROGRAM JACOB2.BAS
30 REM THIS PROGRAM IS DESIGNED TO WORK ONLY WITH HE 380Z-
D CONNECTED BY THE PIO CARD TO THE IP3 PUMP AND THE
RELAXOGRAPH CONNECTED VIA THE SERIAL PORT.
40 '
50 '
60 DIM BLOCK(4,550)
70 REM PARAMETERS LINE NUMBERED 100-500
80 DRUG$="ATRACURIUM"' CHOSEN DRUG
90 WT=70'THE PATIENTS WEIGHT IN kg
100 V$="C"'VERSION OF SOFTWARE IN JACOB.BAS
110 TD=0' THE 4TH TWITCH
120 TA=0' THE FIRST TWITCH
130 REF=0' THE CONTROL TWITCH
140 VOL=50'THE TOTAL VOLUME OF ATRACURIUM SOLUTION
150 F$="DEFAULT"' COMPOSITE FILENAME.
160 MGS=200'THE DOSE OF ATRACURIUM IN mgs IN THE VOLUME
VOL
170 CN=2000' DEFAULT CONCENTRATION OF DRUG IN SYRINGE IN
ug/ml
180 LEV=20' THE DESIRED LEVEL OF T1 FOR CONTROL
190 ST$="OPEN" 'SPECIFIES THE STATE OF THE CONTROL LOOP
200 G1=0.0135' PROPORTIONAL GAIN/KG
210 J=0'COUNTER FOR DISC STORAGE.
220 G2=0.0007' INTEGRAL GAIN/KG
230 IN=0' INITIALISE INTEGRAL TERM
240 ' ARRAY BLOCK CONTAINS TIME, T1,TOF, CODE.
250 R$="" RELAXOGRAPH INPUT STRING
260 A$="" AGE AS CHARACTERS BEFORE CHECKING WITH LEN
270 T1=100' THE STANDARD CONTROL TO TRITCH RATIO
280 TR=100' STANDARD TRAIN OF FOUR
290 TIME=00' THE TIME IN MINS FROM RELAXOGRAPH TIMING
OUTPUT
300 COUNT=0' COUNTS THE NUMBER OF DATA INPUTS AND THE WAY
DOWN BLOCK
310 '
320 '
330 PRINTER 3 'ENGAGES THE PARALELL PRINTER
340 PUT 31
350 LPRINT" AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCKADE
WITH "; DRUG$
360 PUT 31
370 REM TAKE IN BASIC IDENTIFICATION DATA FOR FILENAME
CONSTRUCTION
380 INPUT  "TYPE IN THE PATIENTS THREE INITIALS"; N$
390 IF LEN(N$)> 3 OR LEN(N$)=0  THEN PRINT "INCORRECT
INITIALS - RETYPE" :GOTO 380
400 PUT 31
410 INPUT "TYPE IN THE PATIENTS AGE IN WHOLE YEARS ";A$
420 IF  LEN(A$) > 2 THEN PRINT"AGE RANGE BETWEEN 10 AND 99
ONLY PLEASE":GOTO 410
430 PUT 31
440 INPUT "TYPE IN THE PATIENT'S WEIGHT IN kg "; WT
450 IF WT< 40 OR WT>120 THEN PRINT"WEIGHT <40 OR >120 -
```

```
OUT OF RANGE ": GOTO 440
460 G1=G1*WT
470 G2=G2*WT
480 PUT 31
490 INPUT "TYPE IN THE PATIENTS SEX M OR F "; S$
500 IF LEFT$(S$,1)="M" OR LEFT$(S$,1)="F" THEN GOTO 510
ELSE PRINT"ONLY M OR F ALLOWED": GOTO 490
510 PUT 31
520 INPUT"TYPE IN THE SERIES NO FOR THAT PATIENT 0 - 9
ONLY"; SE$
530 IF LEN(SE$)>1 THEN PRINT " ONE DIGIT ONLY O - 9 PLEASE
": GOTO 520
540 PUT 31
550 F$="B:"+N$+A$+S$+V$+SE$+".DAT"
560 LPRINT" PATIENT AGE "; A$;"yrs WEIGHT "; WT;"kg  SEX
"; S$
570     L P R I N T      "      A C T U A L      O P E R A T I O N
580 LPRINT" SOFTWARE VERSION ";V$;" SERIAL NUMBER OF THIS
RUN ON THIS PATIENT ";SE$
590 PRINT:PRINT"DATA WILL BE STORED ON THE UPPER SURFACE
OF THE LOWER DISC"
600 PRINT:PRINT"INSERT A FORMATTED DOUBLE DENSITY DISC
INTO THE LOWER DRIVE"
610 PRINT:PRINT"PRESS R AS SOON AS YOU HAVE DONE THIS"
620 IF GET(0)<>82 THEN GOTO 620
630 IF LOOKUP(F$)<>0 THEN PUT 31: PRINT"YOUR FILENAME
ALREADY EXISTS ON THIS DISC - CHANGE THE SERIAL NUMBER" :
DIR"B:*.*": GOTO 380
640 '
650 'THE FILE WILL NOW BE OK TO GO ON THE DISC
660 LPRINT " THE FILENAME FOR THIS RUN IS: "; F$
670 PUT 31
680 PRINT "PLEASE ENTER THE TOTAL VOLUME OF SOLUTION IN ml
- A COMMA - THEN THE TOTAL DOSE OF ";DRUG$ ; "IN THAT
SOLUTION"
690 INPUT VOL,MGS
700 CN=MGS*1000/VOL 'CONC OF DRUGS IN THE SYRINGE IN mgs.
710 LPRINT " CONCENTRATION OF "; DRUG$ ;" IS "; CN; "ug/ml
IN "; VOL ;"ml"
720 INPUT "DESIRED LEVEL FOR T1 IN % "; LEV
730 IF LEV >80 OR LEV <5 THEN PRINT "T1 MUST BE BETWEEN 5
AND 80%": GOTO 720
740 LPRINT " DESIRED LEVEL FOR T1 IN THE PATIENT IS
";LEV;"%"
750 LPRINT " PROPORTIONAL GAIN "; G1
760 LPRINT " INTEGRAL GAIN ";G2
770 LPRINT:LPRINT:LPRINT CHR$(15);"COUNT", "TIME", "T1",
"INT", "SPEED","MARK"
780 '
790 '
800 PUT 31
810 PRINT:PRINT "DATA RECEIVING DISC MUST BE IN DRIVE B"
820 PRINT"TYPE R WHEN READY TO COMMENCE AUTOMATIC CONTROL"
830 IF GET(0)<>82 THEN GOTO 830
840 PRINT "AUTOMATIC CONTROL ROUTINE ENTERED"
850 '
860 PRINT"TYPE S TO STOP CONTROL LOOP"
870 PRINT "TYPE R TO RESTART OR A TO ABANDON RUN (DATA
LOST)"
875 PRINT"LOOP IS ";ST$;" PRESS C TO CHANGE CONDITION"
```

```
880 LOOP=GET(100)
890 IF LOOP=ASC("S") THEN GOTO 1710
900 IF LOOP=ASC("R") THEN GOTO 60
910 IF LOOP=ASC("A") THEN END
912  IF  LOOP=ASC("C")  AND  ST$="OPEN"  THEN
ST$="CLOSED":IN=288: GOTO 950
913 IF LOOP=ASC("C") AND ST$="CLOSED" THEN ST$="OPEN"
920 '
930 '
940 REM RELAXOGRAPH OUTPUT READER
950 PRINTER 4,1
960 OPEN #10,"RDR:"
970 INPUT LINE #10,R$
980 CLOSE #10
990 REF=VAL(MID$(R$,29,3))
1000 IF REF<=0 THEN REF= 0.00001
1010 TA= VAL(MID$(R$,13,3))
1020 IF TA<=0 THEN TA=0.00001
1030 TD=VAL(MID$(R$,25,3))
1040 IF TD<=0 THEN TD=0.00001
1050 TR=TD*100/TA
1060 T1=TA*100/REF
1070 MARK = VAL(MID$(R$,9,3))
1080 TIME= VAL(MID$(R$,2,2))*60+VAL(MID$(R$,5,3))
1090 '
1100 '
1110 ' STORE DATA IN THE ARRAY BLOCK
1120 IF TR < 1 THEN TR = 0
1130 IF T1 < 1 THEN T1 = 0
1140 BLOCK(0,COUNT)=TIME
1150 BLOCK(1,COUNT)=T1
1160 BLOCK(2,COUNT)=TR
1170 BLOCK(3,COUNT)=MARK
1180 '
1190 '
1200 'CALCULATE THE BEST FLOW OF BLOCKER IN ML/HR
1230 IN=IN+ (T1-LEV)
1240 SP=(T1-LEV)*G1 +IN*G2
1250 IF SP<=0 THEN SP=0.1
1260 IF SP>99.9 THEN SP=99.9 :PRINT "PUMP AT MAX SPEED"
1265 IF ST$="OPEN" THEN SP=0.1
1270 BLOCK(4,COUNT)= SP
1280 '
1290 '
1300 'IMPLEMENT FLOW ON PUMP
1310 PROC PUMP(SP)
1320 '
1330 '
1340 'PRINT OUT THE DATA
1350 PRINT COUNT, T1,IN, SP, MARK, ST$
1360 PRINTER 3
1370 LPRINT CHR$(15); COUNT, TIME, T1, IN, SP, MARK, ST$
1380 '
1390 '
1400 'TRAP ON COUNT TO AVOID OVERRUNNING ARRAY
1410 ' LOWER END OF THE CONTROL SEQUENCE
1420 IF COUNT=550 THEN GOTO 1710
1430 COUNT=COUNT+1
1440 GOTO 860
1450 '
```

```
1460 '
1470 '**************************START OF PUMP PROC
1480 DEF PROC PUMP (SP), LOCAL X,N,DD,DU,DT
1490 'INITIALIZE PIO
1500 FOR N=1 TO 3
1510 READ X
1520 OUT 34,X
1530 OUT 35,X
1540 NEXT N
1550 DATA 0,15,7
1560 RESTORE
1570 '
1580 '
1590 'APPLY THE VALUE SP TO THE PUMP
1600 SP=SP*10
1610 DD=SP MOD 10
1620 DU=INT(SP/10) MOD 10
1630 DT=INT(SP/100) MOD 10
1640 OUT 33, (DD+DU*16)
1650 OUT 32, DT
1660 PROC END
1670 ' **************************END OF PUMP PROC
1680 '
1690 '
1700 ' ROUTINE TO STORE DATA ON DISC FILE
1710 CREATE#10,F$
1720 QUOTE #10,34
1730 FOR J=0 TO COUNT-1
1740  PRINT#10,  BLOCK(0,J),  BLOCK(1,J),  BLOCK(2,J),
BLOCK(3,J), BLOCK(4,J)
1750 NEXT J
1760 CLOSE #10
1770 '
1780 '
1790 ' FINAL TIDY UP
1800 PROC PUMP(.1)
1810 LPRINT CHR$(27);"@";
1820 END
```

PROGRAM FOR DATA ANALYSIS

```
10 '########################## CALCULATIONS RELY ON A 20S
CYCLE############
20 REM CAPTURE LAST CHANGED 3/JUNE/87
30 PRINTER 3
40 WT=70'PATIENT WEIGHT
50 CN=2000' CONC OF SOLUTION
60 LEV=20''**********************
70 PUT 31
80 PRINT"TYPE IN LEV; PATIENT WT IN KG; SOLUTION CONC IN
UG/ML; THEN RETURN"
90 INPUT LEV, WT, CN
100 N=0' THE EXTENT OF THE DATASET IN THE CONTROLLED
PERIOD
110 C=0' COUNTING THE DATA INTO THE ARRAY
120 MBL=1E20
130 START=0' START OF THE DATA SUBSET
140 TERM=0'  THE MARK NO
150 TX=0'THE ARRAY SUBSCRIPT AT THE END OF THE DATASUBSET
160 S1=0' SUM OF ALL THE X VALUES
170 S2=0' SUM OF ALL THE X*X VALUES
180 S6=0' SUM OF ALL THE DEVIATION VALUES
190 P=0' COUNTER FOR THE POINT COUNT; POINTS ABOVE LEV
200 PC=0' POINT COUNT
210 TD=0' THE TOTAL DOSE GIVEN DURING CONTROLLED SEGMENT
220 DIM BLOCK (4,550)
230 DIR "B:*.*"
240 INPUT "TYPE IN THE FILENAME"; F$
250 LPRINT "FILENAME IS ";F$
260 C=0
270 OPEN #10, F$
280 ON EOF  GOTO 400
290 INPUT #10, TIME, T1,TR, MARK,SP
300 BLOCK(0,C)=TIME
310 BLOCK(1,C)=T1
320 BLOCK(2,C)=TR
330 BLOCK(3,C)=MARK
340 BLOCK(4,C)=SP
360 C=C+1
370 GOTO 290
380 '
390 '
400 C=C-1 'RESETS COUNTER TO TRUE NUMBER OF ITEMS IN ARRAY
ALLOWING FOR 0
401 PUT 31
402 PRINT" DO YOU WANT SEGMENT ANALYSIS OR ROUTINE
ANALYSIS? (TYPE S OR R)"
403 A$=GET$(): IF A$="R" GOTO 430: IF A$="S" GOTO 410:
PRINT"RESPOND ONLY WITH S OR R PLEASE": GOTO 402
404 '
405 '
410 PUT 31
411 PRINT"TYPE IN THE FIRST AND LAST RECORD NUMBERS FOR
YOUR ANALYSIS"
412 INPUT START,TX
413 IF START>TX THEN PRINT"FIRST THEN LAST RECORD NUMBER
PLEASE": GOTO 411
414 IF TX>C THEN PRINT"YOU ARE TRYING TO READ MORE DATA
```

```
THAN YOUVE GOT":GOTO 411
415 LPRINT"SEGMENT ANALYSIS RECORDS ";START;" TO "; TX
416 GOTO 760
418 '
419 '
420 'FIND MINIMUM BLOCKADE LEVEL
430 FOR J=0 TO C
440 IF BLOCK(1,J)<MBL THEN MBL=BLOCK(1,J)
450 NEXT J
460 LPRINT "MINIMUM T1 IN RUN IS ";MBL;"%"
470 '
480 '
490 'FIND POINT AT WHICH T1 CROSSES LEV
500 J=0
510 IF J = C THEN GOTO 580
520 IF BLOCK(1,J) <=LEV THEN GOTO 550
530 J=J+1
540 GOTO 510
550 LPRINT"T1 CROSSED THE SET LEVEL OF ";LEV;"% AT RECORD
NO. "J
560 START=J' THE BEGINNING OF THE DATASET
570 GOTO 630
580 LPRINT" THE T1 NEVER WENT BELOW THE SET LEVEL OF
";LEV;"%"
5 9 0                                                E N D ' # #
##################################################
600 '
610 '
620 'FIND THE END OF CONTROLLED DATASUBSET
630 PUT 31
640 INPUT "TYPE IN THE MARK NUMBER AT WHICH CONTROL IS
THOUGHT TO HAVE STOPPED THEN RETURN";TERM
650 IF TERM <1 OR TERM IS >20 THEN PRINT"MARK NO <1 OR
>20":GOTO 640
660 TX=TERM
670 FOR J=START TO C
680 IF BLOCK(3,J)=TERM THEN TX=J
690 NEXT J
700 IF TERM=TX THEN PRINT" MARK ";TERM;" NOT FOUND   TYPE
IN TERMINAL RECORD NO" : INPUT TX
710 LPRINT "END OF CONTROLLED PERIOD AT RECORD NO. ";TX
720 LPRINT"DURATION OF CONTROLLED PERIOD ";  (TX-
START)/3;"MINS"
730 '
740 '
750 ' ANALYSIS OF THE CONTROLLLED PERIOD RECORDS START TO
TX
760 N=TX-START+1'NCOUNTS INDIVIDUAL READINGS NOT INTERVALS
770 FOR J=START TO TX
780 S1=S1+BLOCK(1,J)
790 S2=S2+ (BLOCK(1,J) * BLOCK(1,J))
800 S6=S6 + (BLOCK(1,J)-LEV) * (BLOCK(1,J)-LEV)
810 TD= TD + (BLOCK(4,J)/180)
820 IF BLOCK(1,J) > LEV THEN P=P+1
830 NEXT J
850 PC=100*P/(TX-START+1)
860 TD=TD*CN*3/(WT*(TX-START))
870 SD=SQR((S2-(S1*S1/N))/(N-1))
880 MEAN=S1/N
885 CV= SQR(S6) * 100 / (LEV * N)
```

```
890 LPRINT"THE MEAN LEVEL FOR T1 IS ";MEAN;"% AND SD IS
";SD; "% CV IS ";SD*100/MEAN;"%"
900 LPRINT"TOTAL DOSE OVER CONTROLLED PERIOD OF ";(TX-
START)/3;"MINS IS ";TD;" mcg/kg/min"
910 LPRINT "PERCENTAGE OF POINTS ABOVE TARGET OF ";LEV;" %
IS ";PC
915 LPRINT "CRITERION VALUE IS "; CV
920 END
```

APPENDIX 2

ABTRACT SUBMITTED TO ARS - NOVEMBER 1987

TOWARDS PRACTICAL AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCKADE WITH ATRACURIUM.

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Automatic control of neuromuscular blockade using pancuronium has already been demonstrated (Asbury and Linkens, 1986) but its use prolonged the anaesthetic preparation period. Our objective was to develop a robust control system which could be used without unduly interrupting the smooth running of a normal theatre list. The system should hold blockade steady at 20% of baseline T1 (determined before administration of relaxant).

A proportional-integral (PI) system, incorporating a preloaded integral, was developed. Proportional and integral gains were derived from step tests using the Ziegler-Nichols (1942) method. The value of the preloaded integral was determined empirically.

The study, which was approved by the hospital Ethical Committee, was carried out in 20 ASA I and II patients undergoing elective surgery. Patients were premedicated with temazepam 20-30 mg. Anaesthesia was induced with fentanyl 50-100 ug and thiopentone 3-4 mg kg^{-1} as appropriate. Baseline T1 readings were obtained with a Datex Relaxograph. Tracheal intubation was accomplished after the administration of atracurium (0.25 mg kg^{-1}) when the T1 had fallen to 25% of baseline. Anaesthesia was maintained with 67% nitrous oxide in oxygen, supplemented by 1% enflurane and fentanyl as indicated.

The Relaxograph measured the EMG at 20s intervals and transferred data to a RML 380Z-D microcomputer. The computer instructed a Vickers IP3 syringe pump to give a flow of atracurium (500 ug ml^{-1}) which was calculated using the PI algorithm and updated every 20s. The quality of control after stabilisation was assessed by calculating a root mean square deviation of points around the target, expressed as a percentage of the 20% target (RMSD). The table summarises the steady state results.

	Range	Mean	SD
Age (yr)	39-78	63	10
Weight (kg)	40-99	64	16
Mean T1 (%)	16.8-21.7	18.9	1.4
Duration (min)	21-77	40.7	16
Dose (ug $kg^{-1}min^{-1}$)	4.2-8.6	5.5	1.2
RMSD (%)	0.3-1.7	1.0	0.4

We conclude that the method provides a degree of relaxation which, after an initial stabilisation period, adheres very closely to the target T1. Blockade is steady enough to allow studies of the possible effect on T1 of other drugs and physiological perturbations such as haemodilution or hypothermia.

Asbury, A.J., and Linkens, D.A. (1986). Anaesthesia, **41**, 316-320.
Ziegler, J.G. and Nichols, N.B. (1942). Trans. ASME, **64**, 759-768.

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