CHAPTER I

INTRODUCTION

Neuromuscular blocking agents interfere with at least one of the steps in the transmission process between the motor nerve ending and the striated muscle. They can be divided into two classes:

a. non-depolarizing agents, which prevent the access of acetylcholine to the end-plate receptors, and

b. depolarizing agents which cause a persisting depolarization of the endplate and therefore rendering the receptors unresponsive to subsequent stimuli.

Both groups do not affect conduction in motor nerves nor do they have a direct action on the contractile mechanism of skeletal muscle fibres.

Chemistry

Most of the muscle relaxants contain two quaternary ammonium groups. The distance between the quaternary nitrogens and the nature of the radicals of these atoms play a very important role in the behaviour of these drugs, thus determining the intensity and duration of therapeutic and unwanted effects.

Clinical use

Both depolarizing and non-depolarizing neuromuscular blocking agents are used in surgical anesthesia. Short-acting drugs like succinylcholine are mainly employed to facilitate endotracheal intubation, bronchoscopy, and short-lasting orthopedic manipulations. Longer-acting drugs like pancuronium and gallamine may be used to provide the muscular relaxation that is necessary for intraperitoneal surgical procedures. They are also used to produce total paralysis of the respiratory muscles in cases where controlled respiration is required (i.e. thoracic surgery, brain surgery). Further they are sometimes employed for diagnostic purposes (myasthenia gravis) and in the treatment of tetanus (Duncalf, 1966). Several muscle relaxants are available for clinical use. Of the non-depolarizing relaxants d-tubocurarine, pancuronium and gallamine triethiodide are employed most frequently. Among the depolarizing drugs, only succinylcholine nowadays finds clinical use as a muscle relaxant.

Pharmacological data

Much time and effort has been spent on studying the effect of muscle relaxants on the neuromuscular junction and other cholinceptive sites so that there is a comprehensive
knowledge of their pharmacodynamic properties. Different species are known to vary markedly in their sensitivity to neuromuscular blocking drugs and therefore the correct choice of an experimental animal is important in testing new relaxant agents. Among the common laboratory animals, the cat was believed to resemble man in its sensitivity, to a wide range of neuromuscular agents. Much less attention has been paid to the pharmacokinetic behaviour of these agents in man and in animals. The lack of quantitative information on the fate of muscle relaxants in vivo is undoubtedly due to the paucity of simple and sensitive methods for the analysis in biological fluids. Until recently most of the quantitative data on the distribution and excretion of these compounds were obtained for d-tubocurarine (Cohen et al. 1965, Cohen et al. 1967) for demethylcurarine (Dal Santo 1964, Marsh 1952) and for gallamine (Feldman et al. 1969) in dogs, while almost all human metabolic studies were carried out with d-tubocurarine (Cohen et al. 1957, Cohen et al. 1965, Kalow 1953, Mahfouz 1949, Marsh 1952) and incidentally with alcuronium (Raafflaub and Frey 1972). Since the introduction of d-tubocurarine (Griffith & Johnson 1942) the first clinically used relaxant in anaesthesiology, numerous quaternary ammonium compounds have been synthesized. Because non-depolarizing agents with a short duration of action are of paramount importance for the anaesthetist, this discussion deals mainly with these. The most important representatives of this group are gallamine, and some developments that are based on a bisquaternary steroid structure, like pancuronium.

**Gallamine**

Gallamine triethiodide - (Flaxedil®) is a synthetic non-depolarizing muscle relaxant with a considerably shorter duration of action than d-tubocurarine (Walts & Dillon 1968). It has been available for clinical use nearly as long as d-tubocurarine. It most widely known side effect is tachycardia but allergic reactions following its use have also been reported. Since the only demonstrated pathway for elimination of gallamine in animals is renal excretion, it has been assumed that in man also renal elimination of this drug determines primarily the duration of action (Churchill Davidson et al. 1967, Anand et al. 1972). Consequently its use in patients with established or potential renal insufficiency, hypovolemia, or in those undergoing bilateral nephrectomy is considered to be contraindicated (McLaughlin 1972). The opposite point of view was, however, expressed by White et al. (1971). From their experience with 17 patients undergoing bilateral nephrectomy they concluded that the duration of action of gallamine does not entirely depend safely be used, in a renal function.

**Steroid muscle relaxant**

A general inter for non-hormonal drug almost rigid support (cf Marshall et al. of mono- and bisquaternary relaxant in clinical compound pancuronium has spread acceptance as in anesthesia and clinical reports on pancuronium of its action and the rapid onset, such as histamine reaction McDowel & Clarke 1967, of claimed rapid onset of this compound for anesthesiologists, the increased incidence (Agoston 1976). This rapid onset and a short duration such as histamine reaction McDowel & Clarke 1967, relative absence of as succinylcholine with non-depolarizing relaxant in the field of the two analogues of pano are differing only in their onset and duration. In spite of the closeness of pancuronium and these in their potency and 1973). In this specific ORG.6368 is very similar onset and duration. However, revealed that were rather long acting in addition, dacuronium was anesthetized patient.

**Aims of the present study**

For the rational above, the two major aims of the present study were: 1. The degree of paralysis produced by pancuronium and its duration of action in normal volunteers. 2. The duration of action and degree of paralysis produced by pancuronium and its duration of action in normal volunteers. The second aim was considered to be more important because in normal volunteers, pancuronium was considered to be less toxic than in patients with heart disease. Therefore, it was considered to be more important to study the fate of this drug in normal volunteers.
Aims of the present study

For the rational clinical use of the compounds mentioned above, the two major properties to be considered are:

1. The **degree of paralysis**, which depends on the affinity of the relaxant to the cholinergic receptor in the end-plate and
2. The **side effects** of the relaxant, which depend on the stability of the drug and its metabolites in the body. If a drug is metabolized too quickly, its duration of action will be limited. Conversely, if it is metabolized slowly, the duration of action may be prolonged. The latter property may be desirable in some situations, such as when a drug is used as a premedication or for long-term treatment. However, it may also be problematic, as prolonged paralysis can lead to complications such as pulmonary atelectasis and urinary retention.

Steroid muscle relaxants

A general interest in the steroid molecule as a skeleton for non-hormonal drugs (Davis 1962) and in particular as an almost rigid support for quaternary ammonium groups (cf Marshall et al. 1973) has led to the discovery of a number of mono- and bisquaternary steroid relaxants. The only steroid relaxant in clinical use is the bigquaternary ammonium compound pancuronium bromide (Pavulon), which has gained widespread acceptance as a useful non-depolarizing muscle relaxant in anesthesia and intensive-care practice. Most of the clinical reports on pancuronium emphasized the safe reversibility of its action and the remarkable absence of side effects, such as histamine release and cardiovascular changes (DTB 1969, McDowell & Clarke 1969, Meyer-Burgdorff & Gerbig 1970). The relative absence of side effects of pancuronium and its claimed rapid onset of action led to the widespread use of this compound for endotracheal intubation. To increase the speed of onset of action, excessive doses of pancuronium were often used for intubation and this certainly contributed to the increased incidence and severity of its side effects (Agoston 1976). This illustrated the need for a drug with a rapid onset and a short duration of action similar to that of succinylcholine without side effects, and the search for better non-depolarizing relaxants therefore continues. Further research in the field of the amino steroids led to the synthesis of two analogues of pancuronium (dacuronium and ORG.6368), differing only in their C-17 substituents (Suppl. II, fig. 1). In spite of the close similarity of the chemical structures of pancuronium and the two compounds, they differ considerably in their potency and/or duration of action in the cat (Sugrue 1973). In this species the neuromuscular block produced by ORG.6368 is very similar to that of succinylcholine in rate of onset and duration. The initial clinical investigations, however, revealed that in man both dacuronium and ORG.6368 were rather long acting (Norman & Katz 1971, Baird 1974). In addition, dacuronium produced persistent tachycardia in anesthetized patients (Norman & Katz 1971).

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hence on its local concentration. It is assumed that the latter is determined by the plasma concentration.

The duration of action, which is mainly determined by the course of the plasma concentration and therefore by the distribution, biotransformation and excretion pattern of the drug.

It should be emphasized that interspecies differences can interfere with the interpretation of these aspects.

These considerations and furthermore the lack of any quantitative data on the fate of pancuronium bromide and gallamine triethiodide in man and the controversial views on the use of gallamine in patients with impaired renal function prompted us to investigate:

1) - the disposition and biotransformation of pancuronium and its analogues as well as the relationship between these metabolic processes and the paralyzing effects of these compounds in the cat.

2) - the metabolic fate of pancuronium bromide and the value of the blood levels of pancuronium as an index of its neuromuscular blocking effects in anesthetized patients.

3) - the metabolic fate of gallamine triethiodide in surgical patients under general anesthesia.
CHAPTER II

EXPERIMENTAL PART

Chemical determination

In the preliminary animal experiments with 14C-pancuronium, a high percentage of the radio-activity was demonstrated in the liver even 5 days after its administration (Van der Veen 1971). The risk of the radiation damage of the liver precluded the clinical use of this radioactive tracer method. We therefore estimated the neuromuscular blocking agents in body fluids in all experiments by a fluorimetric method (Meijer et al. 1971, Kersten et al. 1973) developed in our laboratory, which is a modification of that used by Cohen (1963) to assay d-tubocurarine. The determination is based on complex formation with the fluorescent dye rose-bengal. This method is not specific and estimates metabolites of pancuronium together with the parent compound (Kersten et al. 1973). The fluorescence yield of parent compound and metabolites appears to be the same. The fluorimetric determinations thus indicate the total amount of the bis-quaternary compounds in a sample. Since the 3-hydroxy compound, the only metabolite found in man (Suppl. III), has almost the same neuromuscular blocking activity as the authentic drug in the cat (Sim 1972), the serum concentration values obtained can give relevant information on the levels of active substance. The lowest concentrations which could be detected reliably amounted to 20 ng/mL plasma or serum (there were no differences between the calibration curves prepared for plasma or serum) and 1.5 μg/g tissue. To obtain more information on the biotransformation pattern of pancuronium we have used thin-layer chromatography to separate pancuronium and its metabolites (fig. 1 Suppl. II) (Kersten et al. 1973). In this way semiquantitative data of the proportions of the drugs were obtained by visual comparison. Amounts of 0.5-1.0 μg can be readily visualized on the chromatograms. It was shown (Kersten et al. 1973) that acetylcholine, succinylcholine, neostigmine, edrophonium and other drugs frequently used in surgical patients such as atropine, diazepam, opium alkaloids, thalamonalR, streptomycin and penicillin, do not interfere with the method used in this study. Dacuronium and ORG.6368 were estimated by the same method as pancuronium. This analytical method was also used for the determination of gallamine in serum, bile and urine, but for the determination in serum eosin was used instead of rose-bengal.
Animal experiments with pancuronium

The results of the experiments on the biliary and urinary excretion of pancuronium bromide as well on its serum levels and tissue concentrations in cats are presented in:

Supplement I: The fate of pancuronium in the cat (page 18)

A semilogarithmic plot of the serum concentrations of pancuronium indicates two exponential functions, showing a rapid initial disappearance from plasma with a half-life of 4 min which is followed by a more gradual decline with a half-life of 32 min. In a period of 8 hours, urinary and biliary excretion approximated 30 and 24 per cent of the injected dose respectively, demonstrating an almost equal contribution of the renal and hepatic excretion to the total elimination. A further 24 per cent of the administered dose was recovered from the liver 8 hours after administration of the drug; at that time the serum concentration of the drug was below the detectable level. The kidneys contained only 1% of the administered quantities at that time. In addition these experiments revealed that pancuronium is metabolized in this species; three additional compounds showing RF values identical to those of the reference hydroxy derivatives were identified in urine, bile and in the liver. Approximately 20 per cent of the administered dose was excreted in the form of metabolites, mostly as the 3-hydroxy derivative.

Eight hours after injection, the total recovery of the bisquaternary ammonium compounds approximated 80 per cent of the administered dose. The animal studies with pancuronium were extended when the two closely related analogues dacuronium and ORG.6368 became available. The results of these experiments are presented in:

Supplement II: The relationship between disposition and duration of action of a congenic series of steroidal neuromuscular blocking agents (page 25)

Appreciable amounts of both dacuronium and ORG.6368 were found in the urine, bile and liver 8 hours after their intravenous administration. Various proportions of the injected dose of the respective drugs were metabolized. As in the case with pancuronium, both hepatic and renal routes seem to be of equal importance for the total elimination of these compounds. Despite the very similar chemical structure and physicochemical properties of these drugs the extent of biliary excretion of ORG.6368 differs markedly from that of pancuronium and dacuronium. The difference in the hepatic accumulation of these compounds was even more striking: by the end of an 8-hour observation period 24% of the injected dose of pancuronium, 35% of dacuronium and 51% of ORG.6368 was found in the liver.

Furthermore as early as 10 min after injection the liver contained 27% of the injected dose of pancuronium, dacuronium and ORG.6368 while pancuronium had been excreted in the urine. At the same time the serum concentration of ORG.6368 was below the detectable level; that ORG.6368 is the major route of elimination in the cat (Sugrue 15) and that ORG.6368 is at least partially metabolized in the cat (Dyson 16). In contrast in patients undergoing going cholecystectomy 5 per cent of the injected dose of ORG.6368 was excreted in the bile.

The results of these studies are presented in:

Supplement III: Further investigation of the kinetics of pancuronium with dacuronium and ORG.6368 (page 30)

The disappearance of the bisquaternary ammonium compounds from the blood stream was not significantly different from one another in the dog. On the contrary, the major route of elimination of these compounds was the biliary system. The extent of this excretion varied widely between patients from 20 to 55 per cent of the injected dose. Further biotransformation of these drugs could be identified in total for about 20%.

That in these instances
Furthermore as early as three minutes after drug administration the liver contained 9, 21 and 41% of the injected dose of pancuronium, dacuronium and ORG.6368 respectively. At the same time the serum concentration of ORG.6368 was the lowest while pancuronium had the highest. These facts and the fact that ORG.6368 is the shortest acting compound in this series in the cat (Sugrue 1975) indicate that the brevity of action of ORG.6368 is at least in part dependent on redistribution from post-junctional receptor sites to the liver. In an attempt to eliminate the postulated influence of the hepatic uptake on the duration of action of these drugs, they were injected intra-arterially, close to the tibialis anterior muscle. After the establishment of neuromuscular block of similar intensity, the duration of action of pancuronium appeared to be significantly longer than that of the two newer compounds, indicating that besides hepatic uptake, drug-receptor interaction characteristics influence the duration of action of these drugs. The animal experiments demonstrated appreciable excretion in bile. To obtain information about the kinetics of pancuronium in man it was necessary to study also the biliary excretion of this drug in patients. We therefore studied the kinetics of pancuronium in patients undergoing cholecystectomy with choledochostomy (Group I), cholecystectomy only (Group II) and pelvic operations (Group III). The results of this study are presented and discussed in: 

Supplement III: The fate of pancuronium in man (page 38)

The disappearance of the drug from the plasma proceeded in three phases with half-lives of 5 min, 7-13 min and 108-147 min. Thirty hours after injection the total recovery of the bisquaternary compounds amounted to 37-44 per cent of the injected dose in the urine and to 11 per cent in the bile, indicating that for pancuronium renal excretion represents the major route of elimination in man. Wide individual variations with irregular patterns were seen in the renal elimination of pancuronium in patients undergoing cholecystectomy (Groups I, II). In contrast in Group III the excretion pattern was very similar in all patients. Biliary elimination of the drug also varied widely between patients. Of the three metabolites of pancuronium known from animal studies only one, the 3-OH derivative, could be identified in the urine and bile, accounting in total for about 20 per cent of the administered dose. Further biotransformation of this drug in man cannot be excluded since the recovery of the bisquaternary compounds amounted to 55 per cent of the injected dose at the end of the observation period. Four hours after the injection the mean (pooled values) serum pancuronium concentration was 0.07 ± 0.03 µg/ml. That in these instances no residual muscle paralysis was pre-
sent is not surprising because it has been established that a full reversal from neuromuscular block can be recorded even in the presence of a substantial degree of receptor occupancy by non-depolarizing agents (Waud et al. 1971). This should be borne in mind when post-operative patients are given large doses of narcotic analgesics, diazepam or streptomycin, for respiratory depression may be the result of the additive effects of this residual amount in blood and early post-operative medication. It was therefore desirable to investigate the relationship between blood levels and neuromuscular effects of this compound in surgical patients. The results of this clinical study are presented in:

Supplement IV : The relationship of the serum concentration of pancuronium to its neuromuscular activity in man (page 47).

This relationship has been investigated during recovery from the neuromuscular block produced by 50, 80 and 100 μg/kg doses of pancuronium in anesthetized patients. The time from the start of recovery to the return of the twitch to 25, 50 and 75 per cent of the control value was similar in the different dosage groups but occurred progressively later with increasing doses of pancuronium. At the same time the mean serum concentrations (pooled values) were: 0.13 ± 0.01, 0.11 ± 0.01 and 0.10 ± 0.01 μg/ml (mean ± S.E.M.) respectively. Neuromuscular transmission of the adductor pollicis muscle started to recover at a mean serum pancuronium concentration of 0.21 ± 0.03 μg/ml. Using the serum pancuronium concentration values (corrected for the protein binding of pancuronium) the receptor occupancy, calculated according to Waud et al. (1971), at the time when the twitch contraction was 25, 50 and 75 per cent of control, was 85, 84 and 83 per cent respectively. The same calculation using the post-operative drug concentrations from the previous study (Suppl. III) revealed that about 80 per cent of the receptors were still occupied 4 hours after the administration of the drug. With pancuronium we have found that not only urinary excretion but also biliary elimination and redistribution can terminate the action of a muscle relaxant. In the human experiments with gallamine we have tried to find which of these mechanisms underlies the termination of the effects of this drug. These experiments are described in:

Supplement V : Renal and hepatic elimination of gallamine thiodide in man (page 60).

After a single intravenous injection of 2.5 mg/kg gallamine to patients undergoing cholecystectomy with choledochostomy (Group I), a pelvic operation (Group II) or an orthopaedic operation (Group III) the serum proceeded in the urine 30-48 min and 138-144 results of this study showed that in man too, the excretion of gallamine continued to change and in some patients the gallamine did not seem to be the only compound responsible for the changes in the urine. Therefore, the same experiments were performed in another study with gallamine and pancuronium.
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serum proceeded in three phases with half-lives of 5 min,
30-48 min and 138-144 min in the respective groups. The re-
results of this study showed that not only in animals (Feldman
1969) but in man too, gallamine is primarily excreted un-
changed in the urine. Only negligible amounts of the un-
changed compound were excreted in the bile. However, obser-
vations in some patients indicate that poor urinary excretion
of gallamine does not invariably lead to persistent high
serum concentrations and prolonged paralysis. The most
striking finding in this study was the wide individual vari-
ation in the elimination pattern and in the amount of galla-
mine excreted, especially in patients undergoing biliary
tract surgery, while the plasma decay curves in the three
groups were almost the same. A similar urinary excretion pat-
tern was found with pancuronium in patients undergoing the
same type of operation (Suppl. III). The differences seen
in the urinary elimination pattern between patients who under-
went biliary tract surgery or pelvic and orthopaedic opera-
tions respectively in both studies, indicate that the under-
lying pathology, the degree of surgical stress, and possibly
the patient's age or the combination of these factors may in-
fluence the renal elimination of these compounds. General
anesthetic drugs decrease renal blood flow and glomerular
filtration rate (Freeman 1970) to an extent which is propor-
tional to the depth of anesthesia and the mean blood-pressure
level. However, the glomerular filtration rate tends as a
rule to be more constant than renal blood flow (Weller 1974).
There is reason to assume (Suppl. V), that in patients who
underwent biliary tract surgery, hepato-renal factors could
also be responsible for the decreased urinary excretion of
gallamine and pancuronium.
CHAPTER III

DISCUSSION

Our experimental results fill in some of the gaps which have existed in the knowledge on the fate of muscle relaxants. Pancuronium bromide, at present the only steroid relaxant in clinical use, belongs to the group of non-depolarizing agents. It undergoes slow bio-transformation in both, animal and man. In contrast gallamine is not metabolized to any extent either in animals or in man (Suppl. V). The 3-hydroxy-derivative is the most important metabolite of pancuronium in the cat and it was the only biotransformation product in patients, accounting for about 15% of the administered dose in urine and for 5% in bile. The pharmacological activity of this compound is similar to that of pancuronium in the cat (Sim 1972) but its neuromuscular activity in man is unknown. Renal elimination of pancuronium appears to be the major excretory pathway in mice (Waser 1973), rat (Shindo et al. 1974), dog (Van der Veen 1971) and man (Suppl. III). Our findings in man have been confirmed by Tanaka et al. (1974) and Buzello (1975). In the cat, however, both the hepatic and renal routes seem to be of equal importance, not only for pancuronium, but also for dacruronium and ORG.6368 (Table 1; Suppl. II). Our clinical studies with gallamine have shown that in man this compound is primarily excreted unchanged in the urine. It seems however, that the renal elimination of both pancuronium and gallamine in man might be influenced by underlying pathology or by altered metabolic and/or excretory functions caused by the stress of certain types of surgical procedures (Suppl. V). Biliary excretion of pancuronium appears to be unimportant in the rat both in vivo (Shindo et al. 1974) and in vitro (Meijer & Wetering 1970), but appreciable in man (Suppl. III). In the cat also appreciable amounts, more than 10% of the administered dose of pancuronium, dacruronium and ORG.6368 (Suppl. I and table 1 in Suppl. II) were excreted in bile. Despite their similar physicochemical properties the extent of biliary excretion of ORG.6368 differs markedly from that of pancuronium and dacruronium. Even more striking differences were seen in the hepatic uptake and accumulation of these three steroidal relaxants, suggesting that the ultra-short duration of action of ORG.6368 seen in the cat is regulated primarily by (re-)distribution and may depend largely on its hepatic uptake (Suppl. II). Our studies indicate that the termination of the neuromuscular activity of pancuronium and gallamine mainly depends on redistribution from post-junctional receptor sites to non-specific tissue acceptors after the administration is unlikely that either excretion would significantly affect the duration of action of single modulators. Processes might play a significant role in the interaction of action of one modulator with others. In the search for antagonists of other relaxants, compounds were tested for antagonistic effects in the cat (Sim 1972) and for competitive antagonism in the isohlic: resembling that in man. The antagonistic activity of some steroidal relaxants in the cat is related to the rapid uptake by the liver. It is not unlikely that hepatic uptake of d-tubocurarine is not the only factor regulating the duration of action. In some cases the renal elimination of both pancuronium and gallamine in man might be influenced by underlying pathology associated with the use of these compounds, as shown by Wetering et al. (1975). In the cat, however, both the hepatic and renal routes seem to be of equal importance, not only for pancuronium, but also for dacruronium and ORG.6368 (Table 1; Suppl. II). Our clinical studies with gallamine have shown that in man this compound is primarily excreted unchanged in the urine. It seems however, that the renal elimination of both pancuronium and gallamine in man might be influenced by underlying pathology or by altered metabolic and/or excretory functions caused by the stress of certain types of surgical procedures (Suppl. V). Biliary excretion of pancuronium appears to be unimportant in the rat both in vivo (Shindo et al. 1974) and in vitro (Meijer & Wetering 1970), but appreciable in man (Suppl. III). In the cat also appreciable amounts, more than 10% of the administered dose of pancuronium, dacruronium and ORG.6368 (Suppl. I and table 1 in Suppl. II) were excreted in bile. Despite their similar physicochemical properties the extent of biliary excretion of ORG.6368 differs markedly from that of pancuronium and dacruronium. Even more striking differences were seen in the hepatic uptake and accumulation of these three steroidal relaxants, suggesting that the ultra-short duration of action of ORG.6368 seen in the cat is regulated primarily by (re-)distribution and may depend largely on its hepatic uptake (Suppl. II). Our studies indicate that the termination of the neuromuscular activity of pancuronium and gallamine mainly depends on redistribution from post-junctional receptor sites to non-specific tissue acceptors.
after the administration of single moderate doses. It is unlikely that either biotransformation (if any) or biliary excretion would significantly influence the duration of action of single moderate doses of the drugs. However, these processes might play a considerable role in determining duration of action of large initial or repeated smaller doses. In the search for an "ideal" relaxant drug a wide variety of compounds were tested. All of them showed a short duration of action in the cat (Savarese and Kitz 1973), but their duration of action in the monkey is longer than in the cat, closely resembling that in man. Since the brevity of action in the cat of some steroidal drugs appears to be related to their rapid uptake by the liver (Suppl. II) it seems conceivable that hepatic uptake of these drugs in primates is much slower than in the cat. And although the cat is considered the most suitable experimental model for testing muscle relaxants, it is not reliable for predicting the time course of the effect of these compounds in man. As with other drugs there is no reliable complete substitute for experiments in man. By far the most frequent and important clinical complication associated with the use of non-depolarizing agents is an unduly prolonged effect. In most cases this is attributable to absolute or relative overdose, altered sensitivity of the patient, or a drug interaction (Agoston 1976). It is therefore essential to ensure that the neuromuscular block is completely reversed before the patient enters the recovery room. Our studies with pancuronium (Suppl. IV) and the studies of Matteo (1974) with d-tubocurarine have shown that neuromuscular blocking effects are predictable from serum concentrations. These studies confirmed the in vitro observations of Paton and Waud (1967) and indicated that even after a nearly complete reversal of neuromuscular block as many as 83 per cent of the receptors might be still occupied by the blocking drug. Further calculations indicated that four hours after the administration of a total dose of 6 mg of pancuronium, receptor occupancy might be still 80 per cent (Suppl. III). As already noted, this has obvious clinical implications. An understanding of the relationship between serum concentration and effects of muscle relaxants will increase the predictability of the duration of action of these drugs in patients, and will aid the management of respiratory depression due to prolonged neuromuscular block.
SUMMARY

1. The fate and the relationship between disposition and duration of action of pancuronium and two of its analogues, dacuronium and ORG.6368 have been investigated in the cat. Furthermore the fate of pancuronium, the relationship between its serum concentration and neuromuscular activity and the fate of gallamine triethiodide were studied in surgical patients.

2. These studies revealed that even very closely related steroid relaxants can differ significantly in their pharmacokinetic behaviour. This, in turn, may profoundly change their neuromuscular blocking effects.

3. Due to interspecies differences in drug disposition, the cat does not provide a reliable index of duration of effect in man.

4. Human studies indicate that renal excretion represents the major route of elimination for both pancuronium and gallamine. The latter is excreted unchanged in man, the former undergoes slow biotransformation in both animal and man.

5. Close correlation has been found between serum pancuronium concentration and the intensity of its neuromuscular activity in patients.

References: