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Clinical Pharmacokinetics of Muscle Relaxants

L.B. Wingard and D.R. Cook

Departments of Pharmacology and Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Summary

Muscle relaxants are commonly used as an adjunct to general anaesthesia and to facilitate ventilator care in the intensive care unit. The muscle relaxants are unique in that the degree of neuromuscular blockade can be directly measured. Thus, for some of the muscle relaxants it is possible to correlate the degree of neuromuscular blockade with the plasma concentration of drug. This quantitative pharmacokinetic approach has been applied primarily to d-tubocurarine and to a lesser extent to suxamethonium (succinylcholine), gallamine and pancuronium. The pharmacokinetic information for the other relaxants is mostly descriptive and incomplete.

The variation in drug concentration over time is influenced by the distribution, metabolism and excretion of drug. Metabolism by plasma cholinesterase plays a major role in the termination of action of suxamethonium. Although pancuronium is partly metabolised its major metabolites have moderate pharmacological activity. The other relaxants are excreted through the kidney. For gallamine and dimethyl-tubocurarine, renal excretion appears to be the only means of elimination. However, biliary excretion probably provides an alternative route of elimination for d-tubocurarine and pancuronium. In patients with impaired renal function the duration of neuromuscular blockade may be markedly prolonged following standard doses of gallamine or dimethyl-tubocurarine, may be slightly prolonged following standard doses of pancuronium, and is near normal following standard doses of d-tubocurarine. Following large or repeated doses of pancuronium or d-tubocurarine, the duration of neuromuscular blockade may be markedly prolonged.

Because of their relatively large extracellular fluid volume, infants require more suxamethonium on a weight basis than do adults to produce equal neuromuscular blockade. At a single equipotent dose of suxamethonium, the time to recover full neuromuscular transmission is the same in infants, children and probably adults. Neonates appear to be sensitive to non-depolarising muscle relaxants; dosage criteria are unpredictable.

Reversible neuromuscular blocking agents (muscle relaxants) are used as an adjunct to general anaesthesia and to facilitate ventilator care in the intensive care unit. Muscle relaxants block transmission at nicotinic cholinergic junctions, primarily at the neuromuscular junction. Some agents have minor effects at autonomic ganglia and central nervous system synapses. The 2 types of muscle relaxants, non-depolarising (competitive) and depolarising, act reversibly at these sites (Savarese and Kitz, 1975). The non-depolarising type (e.g. d-tubocurarine, gallamine, pancuronium) act by competing with

acetylcholine for binding to receptor sites on the postjunctional motor endplate; they may have less obvious pre-junctional effects (Galindo, 1971). The depolarising agents (e.g. suxamethonium or succinylcholine, decamethonium) act by a different but as yet unclear mechanism that causes a prolonged change in the sodium and potassium permeability of the postjunctional motor endplate (Savarese and Kitz, 1975).

All these agents have 1 to 3 quaternary ammonium groups and are thus ionised and positively charged, irrespective of the pH. The muscle relaxants are usually administered intravenously. They are rapidly distributed by blood flow and diffusion into the extracellular fluids throughout the body. Transfer of blockers from the plasma to the motor endplate may take place in 7 to 12 seconds (Grob et al., 1956). They do not readily cross the lipoid intestinal wall, blood brain barrier, cell membranes, or placenta. Changes in cardiac output or muscle blood flow can change the speed of onset of neuromuscular blockade (Goat et al., 1976).

The intensity of effect of muscle relaxants can be measured directly by supramaximal stimulation of the ulnar nerve and measurement of the amplitude of resulting thumb adduction, using a force displacement transducer and strip chart recorder (Gissen, 1973; Walts and Dillon, 1968). A typical tracing is shown in figure 1. The ratio of twitch height depression to the maximum possible depression is a measure of the intensity of blockade.

A variety of drugs may modify, usually by enhancement, the neuromuscular blocking effects of the muscle relaxants. Certain antibiotics (e.g. aminoglycosides), local anaesthetics, ganglionic blocking agents, hypokalaemia, and hypermagnesaemia interfere directly with normal neuromuscular transmission (Ali and Savarese, 1976). The effect of the non-depolarising agents is enhanced by potent volatile anaesthetic agents in proportion to the alveolar concentration of anaesthetic agent. For example, at concentrations of 1.25 MAC, halothane, enflurane, and isoflurane significantly reduce the amount of pancuronium and d-tubocurarine required for twitch depression when compared with nitrous oxide anaesthesia (Donlon et al., 1974; Fogdall and Miller, 1975; Miller et al., 1971). At this anaesthetic concentration, enflurane and isoflurane depress neuromuscular transmission more than halothane. (Fogdall.and Miller, 1974; Miller et al., 1971). The mechanism of this potentiation is not known; however, it is presumed to be a postjunctional effect. The effects of inhalational anaesthetics on the duration of nondepolarising block has not been defined. Suxamethonium does not appear to be potentiated by inhalation agents. However, cytotoxic drugs, echothiophate, and hexafluroenium inhibit plasma cholinesterase to one degree or another and thus may prolong the response to suxamethonium (Ali and Savarese, 1976).

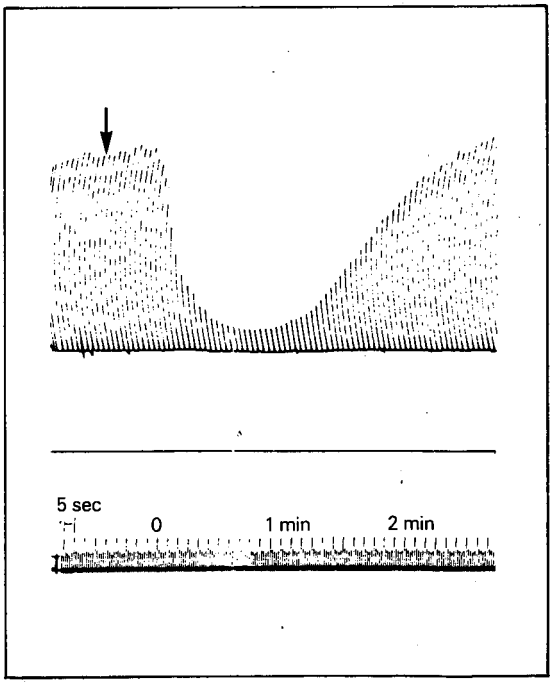

Fig. 1. A recording of evoked thumb adduction made in a patient during nitrous oxide-halothane anesthesia. The single twitch was evoked at 0.15 Hz. At the arrow 4mg/m² suxamethonium was given intravenously. The time course of neuromuscular blockade and recovery can be followed from the time scale.

The time variation in drug concentration in the extracellular fluid, and thus in the degree of neuromuscular blockade, is influenced by the distribution, metabolism and excretion of drug. For some of the muscle relaxants it is possible to correlate the time course of effect to the plasma concentration of drug. The purpose of this review is to summarise how the above factors influence the time course of neuromuscular blockade for the commonly used agents under clinical conditions in humans.

1. Suxamethonium (succinylcholine) Chloride

Suxamethonium, a short acting depolarising muscle relaxant, is a positively charged small linear molecule consisting essentially of two acetylcholine molecules joined together. A typical adult dose of 1.0mg suxamethonium/kg produces complete neuromuscular blockade with recovery to 50% neuromuscular transmission in about 10 minutes following injection (Walts and Dillon, 1967).

1.1 Metabolism

The short duration of action of suxamethonium has been attributed to its presumedly rapid disappearance from the blood. Most of this evidence comes from studies in dogs or *in vitro* measurements with human serum. Lack of a fast, suitable assay has prevented direct *in vivo* measurements of suxamethonium disappearance in humans. Most of the work with suxamethonium has been carried out with C^{14} labelled substrates. Suxamethonium is rapidly hydrolysed *in vitro* by pseudocholinesterase (plasma cholinesterase) to the monocholine metabolite. The latter has about 1/80th the neuromuscular blocking action of suxamethonium and is slowly hydrolysed to succinate and choline (Goedde et al., 1968). At a typical zero order *in vitro* rate of hydrolysis of 27mg suxamethonium/litre of normal human plasma/minute, a dose of 1.0mg/kg would be hydrolysed within 1 minute (Hobbiger and Peck, 1969) in a 70kg patient with 3.5 litres plasma volume.

Recent *in vivo* studies in humans demonstrated suxamethonium in active form in the blood for over 3 minutes (Holst-Larson, 1976). With circulation to the left arm occluded, suxamethonium was injected intravenously into the right hand and the twitch response of both arms monitored for neuromuscular blockade. 3 minutes after injection circulation was restored to the occluded arm and neuromuscular blockade was soon detected. Thus, the *in vivo* rate of hydrolysis of suxamethonium is probably as low as 3 to 7mg/litre/minute (Holst-Larson, 1976). Eger (1974) found that a continuous infusion rate of 4mg suxamethonium/minute was required to maintain a 90% reduction in twitch height in humans. By assuming first order instead of zero order kinetics for the hydrolysis of suxamethonium, these infusion results are in general agreement with the results of Holst-Larson. Perhaps rapid redistribution of suxamethonium contributes to the clinically observed short duration of action.

Although the *in vivo* hydrolysis of suxamethonium by plasma cholinesterase is less rapid than previously assumed, it is still an important factor. About one out of every 2,800 humans has an atypical plasma cholinesterase which hydrolyses suxamethonium at a slower rate than normal (Kalow and Gunn, 1959). In such cases the dose of suxamethonium must be reduced by as much as a factor of 10 or more (Lee-Son et al., 1975).

1.2 Placental Transfer

Little information is available on the placental transfer of suxamethonium in humans. However, studies have been carried out using ^{14}C-suxamethonium in monkeys, where the placenta is similar to that of humans in terms of its functional anatomy. After injection of 2mg/kg into the maternal femoral vein, the fetal monkey concentration of suxamethonium reached a maximum in 5-10 minutes. The maximum fetal concentration was 4%

of that of the maximum maternal concentration following injection into the maternal femoral vein and 12% after injection into the maternal abdominal aorta (Drabkova et al., 1973). In another study, ^{14}C-suxamethonium was injected into the umbilical vein and the distribution of ^{14}C measured in the fetus (van der Kleijn et al., 1973). The ^{14}C was rapidly distributed to the highly perfused organs with a large fraction associated with cartilaginous tissue.

In both monkeys (Drabkova et al., 1973) and humans (Ecobichon and Stephans, 1973), the plasma cholinesterase activity in fetal or premature infant blood was only about half that of adults. The differences appeared due to the quantity of enzyme rather than to enzyme binding properties. However, a dose of 1 mg/kg during obstetric anaesthesia should not endanger the fetus in humans, provided repeated doses are not needed or atypical plasma cholinesterase is not encountered

1.3 Kinetic Characterisation and Models

Although it is not known quantitatively how the plasma concentration of suxamethonium varies with time in humans, useful pharmacokinetic information can be realised by looking at the kinetics of the pharmacological effect. For example, from the work of Eger (1974) it seems that the kinetics of suxamethonium in humans can be approximated by a one compartment model with first order disappearance, to give the following expression:

$$C_O = C \cdot e^{-kt}$$

where C in concentration expressed as the dose or amount of drug D divided by the volume of distribution and k is the first order elimination rate constant. If t_d is the duration of effect, D_d the dose, and D_O the minimum effective dose then the above expression becomes:

$$D_O = D_d \cdot e^{-kt_d}$$

this can be solved for k to give:

$$k = \frac{2.30(\log_{10} D_d - \log_{10} D_O)}{t_d}$$

Levy (1967) applied this expression to data of Walts and Dillon (1967) by plotting the duration of effect versus the $\log_{10}$ of the dose and extrapolating the linear relationship to zero duration to obtain a value for D_O. He then calculated an elimination rate constant k of 0.20min.$^{-1}$ or a $t_{1/2}$ of 3.5 minutes. We have applied the same treatment to the data of Holst-Larson (1976) and obtained a $t_{1/2}$ of 2.7 minutes. These half-lives are in good agreement with the data of Eger (1974).

If the relationship between the intensity of pharmacological effect E and the dose D_O is related log-linearly, then the following expression holds (Levy, 1966):

$$E = m \cdot \log D_O + q$$

where m and q are constants. Combining this with the expression for D_O versus t_d gives the simple expression:

$$E = E_O - \frac{km}{2.30} t_d$$

Here E_O is the intercept at time zero and t_d is the time to whatever percentage blockade is selected. Levy (1967) showed that this expression fits the data of Walts and Dillon (1967) for suxamethonium, thus lending further support to a one compartment model.

1.4 Pharmacokinetics in Infants and Children

The pharmacokinetic properties of suxamethonium have been studied in infants and children. Cook and Fischer (1975) showed that equal doses of suxamethonium on a mg/kg basis gave shorter durations of action in infants as compared with older children. For example, the intensity of

neuromuscular blockade and the duration of blockade were similar for a dose of 1.0mg/kg in infants as with a dose of 0.5mg/kg in children. However, on a mg/m^2 basis the same linear relationship between effect and log dose held for both infants and children. Since body surface area reflects extracellular fluid volume more closely than does body weight, it appeared that the difference on a weight basis was due to the extracellular fluid volume being different with age. Thus, the volume of distribution would differ with age, assuming that plasma cholinesterase levels were near normal. Walts and Dillon (1969) showed no difference between neonates and adults for the duration of effect following an injection of $40mg/m^2$.

The kinetic calculations described earlier for suxamethonium in adults were extended to infants and children (Cook et al., 1976). The elimination half-lives for suxamethonium appeared to increase slightly from about 1.7-1.8 minutes in infants and children to 2.7-4.6 minutes in adults. The results include the data of Holst-Larson (1976). The rates of recovery of neuromuscular transmission, as calculated between 50% and 90% recovery, were highest for children and least for adults. In addition, the minimum effective doses to obtain selected levels of neuromuscular blockade were least in adults and highest in infants, as shown in figure 2. The lateral displacement of the lines in figure 2 may be the result of changes in the volume of distribution or in plasma cholinesterase levels with age. However, additional data will be needed to clarify this issue.

1.5 Summary and Clinical Implications

The *in vivo* rate of hydrolysis of suxamethonium is much less than that based on *in vitro* measurements and suxamethonium most likely exists in active form within the circulation for at least 3 minutes. The plasma kinetics of suxamethonium can be reasonably well approximated by a one-compartment model with a first order elimination half-life of 2 to 4 minutes.

On a mg/kg basis it takes less suxamethonium to obtain a desired degree of neuromuscular blockade as the age of the subject increases, with infants requiring more than children or adults. The explanation for this trend may lie in changes in the relative volumes of extracellular fluid or the relative amounts of plasma cholinesterase in the different age groups.

The need exists for more *in vivo* studies in humans, perhaps in subjects with atypical plasma cholinesterase in order to slow down suxamethonium degradation, so as to relate the degree of neuromuscular blockade to the actual plasma levels of the drug. In addition, the possible binding of suxamethonium to plasma proteins or to cartilage type tissues (as noted with tubocurarine) should be re-evaluated in order to better assess the apparent volume of distribution of the drug. The relative rates of transfer by diffusion through capillary walls and hydrolysis also need to be determined more accurately in order to explain more

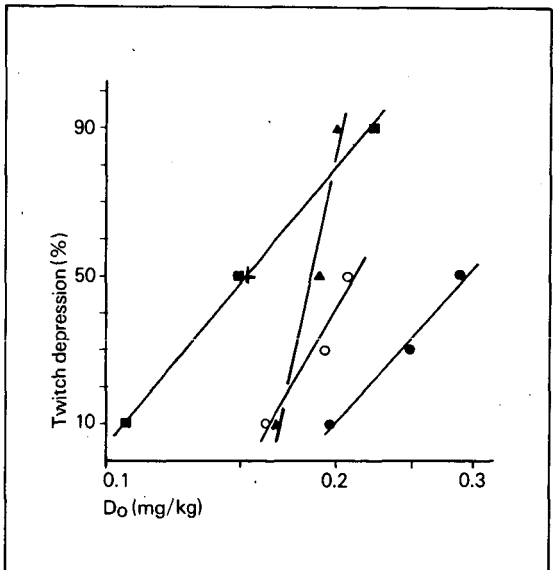

Fig. 2. Extent of blockade of neuromuscular transmission as a function of the minimum effective dose to obtain each level of blockade. Symbols are experimental data: ● infants and ○ children (Cook and Fischer, 1975); ■ adults (Katz and Ryan, 1969); ▲ adults (Walts and Dillon, 1967); † adults (Holst-Larson, (1976). Lines are linear least square fits. Adapted from Cook et al. (1976).

clearly the rate limiting factors in the dynamics of neuromuscular blockade with suxamethonium.

2. *d-Tubocurarine Chloride*

Until recently d-tubocurarine was described as a bis-quaternary ammonium compound. However, there is evidence to support a mono-quaternary ammonium structure (Everett et al., 1970).

2.1 Plasma Levels and Effect

A typical adult dose of 0.30mg d-tubocurarine produces complete non-depolarising neuromuscular blockade, with a duration of about 51 minutes from intravenous injection to 50% recovery of neuromuscular transmission, and 74 minutes to 90% recovery (Walts and Dillon, 1968). The duration of blockade appears to depend simply on how long it takes the concentration of drug in the extracellular fluid to diminish to a particular value.

Matteo et al. (1974) used a very sensitive radioimmunoassay for d-tubocurarine and found a highly significant linear correlation between the degree of neuromuscular blockade in humans and the serum concentration of drug. In adults, a minimum concentration of 0.2μg/ml was needed before any blockade developed and 0.7μg/ml was needed for complete blockade. These concentrations agreed very closely with those calculated assuming a d-tubocurarine-receptor binding constant of 10^{-7} M and assuming 90% or 75% of the motor endplate receptors were occupied by d-tubocurarine for essentially complete or minimum detectable blockade, respectively (Waud, 1975).

These studies support the theory that the d-tubocurarine-receptor complex dissociates to give unbound d-tubocurarine and free the receptors, as the concentration of drug in the serum and extracellular space is decreased by drug elimination. Feldman and Tyrrell (1970) proposed that the d-tubocurarine-receptor complex dissociates only when acetylcholine molecules 'push' the bound d-tubocurarine off the receptors. However, the experimental evidence in support of this is far from convincing. The pharmacokinetic considerations inherent in the experimental method provide alternate explanations (Waud, 1975).

2.2 Distribution and Elimination

Although there are data about the distribution and elimination of d-tubocurarine in animals, the distribution and fate of the drug in humans is still uncertain. Most of this uncertainty has been due to the use of assays of insufficient sensitivity or selectivity for d-tubocurarine.

2.2.1 Elimination and Renal Function

Kalow (1953) reported that 33% of a dose of d-tubocurarine appeared as unmetabolised drug in the urine in 10 to 15 hours after injection. This was later increased to 60 to 70% by collecting urine for 24 hours; however, no data were presented to substantiate this claim (Fleischli and Cohen; 1966). The apparent major importance of renal function for excretion should be reflected in a prolonged duration of neuromuscular blockade in patients with renal failure given the same dose as administered to patients with normal renal function. However, in 6 patients with no renal function and undergoing abdominal surgery there was no prolongation of effects of d-tubocurarine after a dose of 0.42 to 0.95mg/kg (Churchill-Davidson et al., 1967).

Although some authors have claimed that d-tubocurarine is also eliminated through the bile, no experimental data from humans has been presented to validate this claim (Fleischli and Cohen, 1966). In dogs receiving 0.3mg/kg d-tubocurarine about 11% of the injected dose was eliminated in the bile in 24 hours; this was increased to 39% with ligation of the renal pedicles (Cohen et al., 1967). Whether or not this alternate mechanism for elimination of d-tubocurarine is of major importance in humans remains to be demonstrated. However, cases of

prolonged paralysis have been reported following use of large doses of d-tubocurarine in patients with renal failure (Homi and Smith, 1970; Riordan and Gilbertson, 1971). Presumably, elimination of d-tubocurarine through the bile is dose dependent; with sufficiently large or excessive repeated doses of d-tubocurarine, elimination through the bile is also prolonged. More recently, 4 cases of postoperative respiratory failure were reported in patients with renal failure following reversal of d-tubocurarine blockade by neostigmine (Miller and Cullen, 1976). Large doses of d-tubocurarine had been used (48 to 55mg in total). Since no blood samples were taken, it was not clear whether the respiratory problems were due to elevated plasma levels of d-tubocurarine or to other complications present. In a more definitive study, in which blood samples were taken and assayed for d-tubocurarine by the radioimmunoassay technique, the duration of effect and the relationship between effect and serum concentration of the drug were about the same in 10 normal patients as compared with 10 others with renal failure after a dose of 0.3 or 0.5mg/kg d-tubocurarine (Miller and Matteo, 1976). The serum concentration of d-tubocurarine versus time curves were essentially parallel for normal subjects and patients with renal failure indicating that the clearance of d-tubocurarine occurred at the same rate in the 2 groups. In 5 patients with newly transplanted kidneys the ability to eliminate d-tubocurarine in the urine was markedly reduced. The data suggest that there is an alternative pathway for elimination of d-tubocurarine in humans following usual doses in renal failure, but that prolongation of blockade may occur after large or repeated doses.

2.2.2 Distribution

d-Tubocurarine undergoes rapid distribution to plasma proteins, extracellular fluid and the tissue of major organs. After intravenous injection of 0.3mg/kg, the concentration of d-tubocurarine in muscle tissue reached a maximum within 5 minutes (Cohen et al., 1965). Similarly, significant levels of d-tubocurarine appeared in the lumbar cerebrospinal fluid within 15 minutes of a dose of 0.43 to 0.68mg/kg (Devasankaraiah et al., 1973). With a dose of 0.3mg/kg, the plasma or serum concentration of d-tubocurarine declined rapidly during the first 10 minutes due to the initial distribution to extracellular fluid, tissue, and plasma proteins. This was followed by a period of about 60 minutes of combined redistribution and elimination; a third period of monoexponential disappearance from plasma with a half-life of 150 minutes was also observed (Horowitz and Spector, 1973). Although the serum or plasma d-tubocurarine concentration decay curves were essentially parallel among individual patients, the curves differed in their concentration at time zero (Horowitz and Spector, 1973; Miller and Matteo, 1976). This shift in initial concentration reflected differences in the apparent volume of distribution of d-tubocurarine among individuals.

2.3 Protein Binding

At a plasma concentration of 5μg/ml d-tubocurarine, about 44% is bound to plasma proteins, as determined by equilibrium dialysis, and 82 to 90% to gamma globulin, using electrophoresis (Ghoneim et al., 1973). In a more detailed study employing tritiated d-tubocurarine 15% of the drug was bound to gamma globulin and 24% to albumin using equilibrium dialysis, and 82 to 90% to gamma globulin using electrophoresis; the reason for this difference is not understood (Ghoneim and Pandya, 1975).

A loose correlation between the required dose of d-tubocurarine and the serum level of gamma globulin was observed in 50 patients undergoing lower abdominal surgery for gynaecological cancer (Stovner et al., 1971). In related work d-tubocurarine dimethyl-^{14}C-ether iodide was about 40% bound to human plasma proteins over the concentration range of 0.006 to 8.8μg/ml and was also bound in appreciable amounts to chondroitin sulphate and cartilage (Olsen et al., 1975). These connective type materials may also be a binding site for d-tubocurarine. It appears that at least 40 to 50% of d-

tubocurarine is bound to plasma proteins at concentrations greater than those found clinically and that variations in the gamma globulin level may account for differences in the amount of drug bound among individual patients.

2.4 Placental Transfer and Use in Neonates

d-Tubocurarine can be used during obstetrics and in neonates; although it does cross the placenta in small amounts. Within 10 minutes after maternal injection in humans the level of ^{14}C-dimethyltubocurarine in the umbilical vein reached 12% of the maternal venous level (Kivalo and Saarikoski, 1976).

A dose of about 0.25mg/kg can be used safely in neonates at birth with up to 0.50mg/kg at 28 days of age (Bennett et al., 1976). This agrees with other reports that newborns are more sensitive than children and adults to d-tubocurarine Walts and Dillon, 1969; Long and Bachman, 1967). This greater sensitivity of newborns to d-tubocurarine did not appear due to differences in the serum albumin or serum globulin levels in 50 neonates aged 1 to 23 days (Vivori et al., 1974). Part of this difference in sensitivity to d-tubocurarine may be due to changes in the proportion of extracellular water or lean body mass with age; and some authors have suggested that d-tubocurarine doses should be based on body surface area instead of body weight (Wulfsohn, 1972).

2.5 Kinetic Characterisation and Models

The apparent volume of distribution of d-tubocurarine, based on the dose divided by the total plasma or serum concentration of drug (protein bound plus unbound) at time zero, is about 2.4 to 3.0 litres (Wingard and Cook, 1976)). Increased plasma protein binding of d-tubocurarine results in a larger total concentration at time zero, assuming that the concentration of unbound drug stays the same, and, therefore, a smaller volume of distribution.

The importance of a different apparent volume of distribution in explaining interindividual variation in the duration of neuromuscular blockade was shown using computer simulations (Wingard and Cook, 1976). The time variation of the serum d-tubocurarine concentration data of Horowitz and Spector (1973) was fitted to an equation of three exponentials. This was combined with the linear relationship of Matteo et al. (1974) between effect and serum concentration of d-tubocurarine to give the following expression for the variation of the percent recovery of neuromuscular transmission with time:

$$R = 146 - 212\frac{D}{V_d}(0.774e^{-0.741t} + 0.172e^{-0.0704t} + 0.0838e^{-0.00456t})$$

where D is the dose in mg, V_d the apparent volume of distribution in ml, and t the time in minutes.

A comparison of the simulated and experimentally determined duration of effect values are shown in figure 3 for different values of the d-tubocurarine serum concentration C_0 at time zero. The C_0 values calculated as D/V_d, are influenced both by the selected dose and the apparent volume of distribution. Thus, a dose of 0.3mg/kg in a 70kg person should produce a C_0 of 7.0 to 8.75μg/ml for a V_d of 2.4 to 3.0 litres. The corresponding duration of effect, as measured to 50% recovery of neuromuscular trasmission, would be 63 and 107 minutes for a V_d of 2.4 and 3.0 litres, respectively. Therefore, a rather wide range of recovery times can be expected for a given dose, depending on the apparent volume of distribution of d-tubocurarine in a particular patient.

The slopes of the curves in figure 3 decrease with increasing value of C_0, indicating that the time to decline to a particular serum concentration of d-tubocurarine is not directly proportional to C_0. This is in agreement with clinical observations in that the duration of action is not proportional to the dose, particularly when booster injections are given during surgery.

An earlier pharmacokinetic model for dTC was constructed assuming 42% of the drug was eliminated unchanged in the urine (Gibaldi et al., 1972a). This model gave abnormally high recovery times for patients with renal failure (Gibaldi et al., 1972b); Miller and Matteo, 1976.

2.6 Summary and Clinical Implications

There is obviously an alternate pathway to the kidneys for the elimination of d-tubocurarine in humans since little or no prolongation of blockade is observed in patients with impaired renal function as compared with patients with normal renal function following usual standard doses, but prolonged paralysis may occur after large or repeated doses. Although the biliary route has been suggested as an alternate excretory pathway, this has not been verified experimentally in humans; and a control mechanism for establishing a biliary to renal elimination ratio has not been suggested.

Although the mechanisms of elimination of d-tubocurarine are still unclear, the degree of neuromuscular blockade seems to depend simply on the concentration of d-tubocurarine in the extracellular fluid at the neuromuscular junction. The serum d-tubocurarine decay time in turn is dependent on the dose as well as the apparent volume of distribution which is of the order of 2.4 to 3.0 litres. d-Tubocurarine is about 44% bound to serum proteins, with albumin and gamma globulin the major proteins involved. This aspect needs to be studied further by carrying out serum d-tubocurarine decay curves on individual subjects to see how the volume of distribution and time zero drug concentrations can be related to the duration of effect.

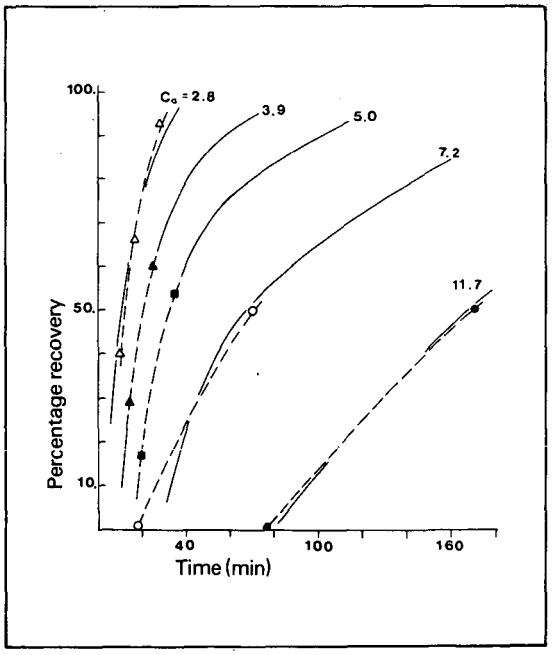

Fig. 3. Simulated (solid lines) and experimental (points and dashed lines) time course of percentage recovery R of neuromuscular transmission after a single dose of d-tubocurarine in humans. C_0 is the dose divided by the apparent volume of distribution. Experimental points are: ○ 0.3mg/kg and ● 0.6mg/kg (Matteo et al., 1974); △ 4.0mg/m² (0.098mg/kg); ▲ 5.6mg/m² (0.15mg/kg); ■ 8.0mg/m² (0.20mg/kg) [Walts and Dillon, 1968].

3. Pancuronium Bromide

Pancuronium is a steroidal bis-quaternary ammonium compound with about 5 times the potency of d-tubocurarine. A typical adult dose of 0.05mg/kg produces complete neuromuscular blockade with recovery to 50% in 37 minutes (Normal et al., 1970).

3.1 Metabolism

The primary difficulty in determining the pharmacokinetics of Pancuronium has been the lack of a sensitive assay specific for unmetabolised drug. The active compound contains acetate ester groups at the number 3 and 17 positions on the steroid ring. These ester groups undergo hydrolysis to the mono- and dihydroxy metabolites. The mono-hydroxy form possesses some muscle relaxant activity, but the dihydroxy form is inert (Buzello, 1975).

3.2 Plasma Levels and Elimination

One pharmacokinetic study used an assay consisting of extraction, thin layer chromatographic separation of pancuronium from metabolites, and quantification of the amount of pancuronium by spectrophotometry (Buzello, 1974). However, this assay had a reported sensitivity of only 1 to 2μg pancuronium/ml serum using 10ml of serum; yet it was used to report concentrations of as low as 0.1μg/ml (Buzello, 1975). Thus, the results must be viewed only as approximations. In this study 9 patients received a dose of 0.13mg/kg. Within 1 minute after injection the serum level of pancuronium was 2.2μg/ml. This decreased to 1.1μg/ml in about 5 minutes. A serum pancuronium concentration of 0.1 to 0.3μg/ml was reached in 120 minutes, at which time the muscle relaxation had ended.

Using Buzello's data, we estimated that a 3-compartment model was needed to fit the serum decay curve. The half-life of the terminal portion was 110 minutes, similar to that of d-tubocurarine. The apparent volume of distribution of 3.2 litres also approximated that of d-tubocurarine. These data are consistent with the hypothesis that the degree of blockade depends on the concentration of pancuronium in the vicinity of the motor endplate receptors.

Buzello (1975) also reported that 50% of a dose of 0.08mg/kg pancuronium was eliminated in the urine within 12 hours; 40% as unchanged drug and 10% as metabolites, and that no additional renal elimination occurred during the subsequent 60 hours. Over the 24 hour period following injection, about 10% of the dose was eliminated through the bile.

Agoston et al. (1973) used florimetry to measure the total pancuronium plus metabolites and then employed thin layer chromatography followed by visual comparison of the spot intensity with reference spots for a semiquantitative estimation of pancuronium concentrations. These data also must be considered as approximations. The results from 20 patients receiving 0.095mg/kg pancuronium showed 37 to 44% of the dose to be eliminated in the urine and 11% excreted in the bile over the 30-hour period following injection. About 20% of the dose appeared in the urine as the 3-hydroxy derivative. The validity of the pharmacokinetic analysis for the data during the first hour after injection is highly questionable; however, the half-life of 108 to 147 minutes reported for the slowest phase is in agreement with the results of Buzello (1975).

3.3 Elimination and Renal Function

Since a large fraction of pancuronium is eliminated by renal excretion, patients with reduced renal function should show slower elimination and prolonged duration of neuromuscular blockade for the same dose as compared with normal subjects. This was demonstrated using a group of 6 normal adults (0.93mg/100ml plasma creatinine) and 7 patients with chronic renal failure (9.4mg/100ml plasma creatinine). The fluorimetric assay used in the study was not specific for unmetabolised pancuronium, so that the results were only semi-quantitative (McLeod et al., 1976). The clearance rate of pancuronium plus metabolites from the plasma was 74ml/min for the normals and only 20ml/min for the group with impaired renal function. In another study (Miller et al., 1973), the duration of blockade, as measured from injection to 5% recovery of transmission, was prolonged by 20 minutes in 15 patients with renal failure as compared with 15 patients with normal renal function after a dose of 1.2 to 3.6mg pancuronium/m^2 (about 0.03 to 0.09mg/kg). Prolongation of pancuronium blockade in patients with renal failure has also been reported by Stojanov (1969) and Miller and Cullen (1976).

3.4 Protein Binding

Although several earlier reviews have indicated that pancuronium does not bind to plasma proteins, there is now definitive evidence to show that signifi-

cant binding does occur. The measurements were made *in vitro* with ^{14}C-pancuronium and human serum using an ultrafiltration technique (Thompson, 1976). At clinical levels of 1 to 2mg/ml serum only about 13% of the serum concentration of pancuronium was not bound and *in vivo* would be free to pass into the extracellular space or through the renal glomeruli. Pancuronium was bound strongly to gamma globulin and albumin, but not to alpha globulin or beta globulin. One would expect that the apparent volume of distribution for pancuronium would vary with the gamma globulin and albumin levels, as observed for d-tubocurarine, and in turn markedly influence on the duration of blockade. However, to date no reports on this expected relationship have been made.

3.5 Placental Transfer

Pancuronium does not appear to cross the human placenta in appreciable quantities based on data using the non-specific assays (Heaney, 1974; Speirs and Sim, 1972). None of the infants born of mothers after the use of pancuronium in caesarean sections showed any clinical evidence of neuromuscular blockade (Forgacs, 1970; Speirs and Sim, 1972).

3.6 Summary and Clinical Implications

The plasma or serum decay rates as well as the apparent volume of distribution appear to be fairly similar for equipotent doses of pancuronium and d-tubocurarine. As with d-tubocurarine, the level of blockade appears to correlate with the plasma level of pancuronium. About 50% of a dose of pancuronium is eliminated in the urine, with up to 20% as metabolites and the remaining 30% or more as unchanged pancuronium. Another 10% is eliminated through the biliary route; although this does not appear to be a particularly important pathway since patients with chronic renal failure definitely show prolongation of neuromuscular blockade with pancuronium.

There is a need for a highly sensitive assay, selective only for pancuronium and not the metabolites, to validate or correct the present pharmacokinetic studies done with only semi-quantitative or non-selective assays. In addition, the report that pancuronium *in vitro* is strongly bound to serum gamma globulin and albumin so that only 13% is not bound at therapeutic levels, needs to be followed-up to determine what fraction of pancuronium is bound *in vivo*.

4. Gallamine Triethiodide

Gallamine is a non-depolarising relaxant that contains three quaternary ammonium groups. At a dose of 36mg/m^2 the blockade is 88% complete with recovery to 50% transmission in 23 minutes (Walts and Dillon, 1968).

Relatively little is available on the pharmacokinetics of this neuromuscular blocking agent in humans. The fate of gallamine in humans has not been established definitely; although through indirect evidence it seems that an appreciable fraction of the dose is eliminated unchanged through the kidneys. In the dog, 84% of a dose of 2mg/kg radiolabelled gallamine was excreted unchanged by the kidneys in 24 hours, while only 4% was found in the bile in 12 hours. When the renal pedicles were ligated, the blood concentration of gallamine remained elevated for over 24 hours; and only 0.9% of the dose was recovered in the bile for the same time span. Thus, there does not appear to be an alternate elimination pathway for gallamine in the dog (Feldman et al., 1969). These same elimination criteria most likely apply in humans as well, since 5 patients with renal failure showed significant prolongation of blockade during abdominal surgery under gallamine-aided anaesthesia (Churchill-Davidson et al., 1967). Numerous other reports describe prolongation of blockade following use of gallamine in patients with renal failure (see Prescott, 1972).

Gallamine binds to plasma proteins, but the degree of binding both *in vivo* and *in vitro* is unclear. Gallamine binding to beta and gamma globulins was observed *in vitro* using an electrophoretic technique (Skivington, 1972); while a very weak correlation between gallamine requirements in mg/m^2 and serum albumin concentration was noted for 100 patients undergoing abdominal surgery (Stovner et al., 1971).

It is of interest that in the dog, complete blockade with gallamine appeared to remain until the blood level of gallamine was reduced to 3.8μg/ml, and the blockade ended at a plasma gallamine level of 1.9μg/ml (Feldman et al., 1969). This supports, but certainly in no way proves, the theory that the degree of blockade depends simply on the concentration of muscle relaxant at the neuromuscular junction.

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Author's address: Dr *David R. Cook*, 125 DeSoto Street, Pittsburgh, *PA 15213* (USA).