Université de Montréal

Pharmacokinetic-pharmacodynamic modeling of doxacurium: effect of input rate

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ABSTRACT

One of the basic assumptions in pharmacokinetic-pharmacodynamic modeling (PK-PD) is that drug equilibration rate constant between plasma concentration and effect (Keo) is not changed by input rate. In order to test this assumption in a clinical setting, a 25µg/kg IV dose of doxacurium was administered either by bolus injection or 10 min-infusion to fifteen anaesthetized patients. Neuromuscular function was monitored using train-of-four stimulation of the ulnar nerve. For the short infusion dose, arterial concentrations were measured at 1-min intervals during infusion and at frequent intervals thereafter. Following the IV bolus dose, the early PK profile of doxacurium was investigated by measuring doxacurium arterial concentrations every 10 seconds during the first 2 minutes and at frequent intervals thereafter. PK-PD modeling was performed using non-parametric approach with and without including a finite receptor concentration (R_{tot}) in the effect compartment. Kinetic parameters were unchanged. For the bolus and the infusion, Keo values were 0.053 ± 0.006 min^{-1} and 0.056 ± 0.009 min, respectively. Using the Rtot model, corresponding Keo values were 0.148 ± 0.016 and 0.150 ± 0.024, respectively. The relatively faster Keo obtained with the Rtot model is compatible with the high potency of doxacurium. In conclusion, our results show that PK-PD parameters derived with either a bolus or an infusion mode of administration, are equally reliable.

RÉSUMÉ

Une des présuppositions de base en modélisation pharmacocinétique-pharmacodynamique (PK-PD) est que la constante de la vitesse d'équilibre entre les concentrations du médicament dans le compartiment central et celles du compartiment effet (Keo) n'est pas influencée par la vitesse d'entrée du médicament dans le compartiment central. Or, une courte infusion est généralement choisie pour effectuer les études PK-PD, même si les bloqueurs neuromusculaires sont le plus souvent administrés sous forme d'un bolus en pratique clinique. Ce mode d'administration est préféré parce qu'il est plus facile de prélever suffisamment d'échantillons sanguins pendant l'installation de l'effet relaxant.

Récemment, des études effectuées dans notre laboratoire ont démontré qu'un échantillonnage artériel intensif pendant les deux premières minutes suivant l'administration d'un bolus permettait de bien caractériser la relation PK-PD de certains bloqueurs neuromusculaires, en l'occurrence, le vécuronium et l'atracurium. Toutefois, les valeurs de Keo sont généralement plus lentes que celles obtenues après une courte infusion. D'autre part, lorsque le modèle traditionnel est modifié par l'addition d'une concentration prédéterminée de récepteurs (Rtot) dans le compartiment effet, les valeurs de Keo du vécuronium se

rapprochent de beaucoup de celles obtenues après une courte infusion alors que celles de l'atracurium ne sont pas affectées. Par conséquent, l'occupation des récepteurs semble être un facteur limitant pour le vécuronium, un médicament à puissance élevée, mais non pour l'atracurium. Ces résultats nous ont amenés à remettre en question la pré-supposition de base concernant la vitesse d'entrée dans le compartiment central sur la relation PK-PD.

L'objectif primaire de la présente étude était de déterminer si la vitesse d'administration d'un médicament, i.e. un bolus vs une infusion courte, a un impact sur l'estimation de la vitesse Keo dans un context clinique. L'objectif secondaire était de comparer les paramètres PK-PD obtenus avec ou sans le modèle Rtot. Le doxacurium a été choisi comme médicament-modèle parce que, à la lumière des résultats antérieurs, l'occupation des récepteurs semble jouer un rôle important dans la vitesse d'installation de l'effet chez les médicaments à puissance élevée seulement.

Après l'adoption du protocole clinique par le Comité d'éthique de l'Hôpital Hôtel-Dieu de Montréal, les patients ont tous signé un formulaire de consentement éclairé avant d'être inclus dans l'étude. L'âge de ces patients variait de 20 à 62 ans, leur poids se situait en deça de 25% de leur poids idéal, et leur état physique correspondait à la classe ASA I ou II de l'American Society of Anesthesiologists. L'anesthésie a été induite avec l'alfentanil (20 - 30 ug/kg) et le propofol (1.5 – 3 ug/kg) et maintenue avec un mélange 70 : 30 d'oxyde nitreux et d'oxygène et par

une infusion continue de propofol (10 – 15 mg/kg/hr). L'intubation trachéale a été effectuée sans relaxant musculaire. Le monitoring de la fonction neuromusculaire s'est fait en mesurant la force de contraction de l'adductor pollicis en réponse à une stimulation supramaximale en train de quatre (2 Hz pour 2 sec toutes les 20 sec) du nerf ulnaire au niveau du poignet à l'aide d'électrodes de surface. Après stabilisation, une dose intra-veineuse de 25 ug/kg de chlorure de doxacurium a été administrée sous forme d'un bolus (n = 8) ou d'une infusion de 10 minutes (n = 7). Pour le bolus, le profil pharmacocinétique « immédiat » a été caractérisé en déterminant les concentrations artérielles de doxacurium à toutes les 10 secondes pendant les 2 premières minutes et à de fréquents intervalles pendant les 5 heures suivantes. Pour l'infusion courte, les échantillons artériels ont été prelevés à 1 minute d'intervalle pendant l'infusion et aux mêmes intervalles par la suite. Les concentrations plasmatiques de doxacurium ont été mesurées à l'aide d'un appareil de chromatographie liquide à haute performance couplé à un détecteur ultra-violet. La modélisation de la relation PK-PD a été effectuée en utilisant une approche non paramétrique avec ou sans inclusion d'une concentration prédéterminée de récepteurs (Rtot) dans le compartiment effet.

Premièrement, tel qu'attendu, aucune différence n'a été observée au niveau des paramètres pharmacocinétiques du doxacurium pour les deux types d'administration. De plus, les valeurs de la constante d'équilibre Keo pour le bolus et la courte infusion étaient semblables, soit : 0.053 ± 0.006 min $^{-1}$ et 0.056 ± 0.009 min^{-1}, respectivement. Ces résultats viennent confirmer que la vitesse

d'entrée du médicament dans le compartiment central n'a aucune influence sur la détermination des paramètres PK-PD. Deuxièmement, nos résultats indiquent que l'ajout d'une concentration donnée de récepteurs au modèle affecte de manière identique les valeurs de Keo pour le bolus et la courte infusion, qui deviennent 0.148 ± 0.016 et 0.150 ± 0.024 min^{-1}, respectivement. Cette augmentation de la vitesse d'équilibre par le modèle Rtot est compatible avec la puissance élevée du doxacurium. En conclusion, nos résultats indiquent qu'il est tout aussi valable de déterminer les paramètres PK-PD du doxacurium après administration d'un bolus que d'une courte infusion.

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LIST OF ABBREVIATIONS

γ	The slope factor of sigmoid curve
ACh	Acetylcholine
AChE	Acetylcholinesterase
ASA	American Society of Anesthesiologists
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 to infinite
AUMC	Area under the first moment plasma concentration-time curve
Ce	Drug concentration in effect compartment
CL	Total body clearance
Cmax	Maximum plasma concentration
Cp	Drug concentration in central compartment (plasma)
Ce_u	Concentration of free drug in effect compartment
E	Effect
EC50	Effect compartment concentration of drug at 50% effect
ED50	Dose at 50% effect
ED95	Dose at 95% effect
Emax	Maximum effect
EMG	Electromyography
HPLC	High Performance Liquid Chromatography
IV	Intravenous

K_{eo}	Equilibrium rate constant between plasma concentration and effect
MMG	Mechanomyography
MRT	Mean residence time
MSQU	Mean of squared residuals
N_2O	Nitrous oxide
NMJ	Neuromuscular Junction
PD	Pharmacodynamics
PK	Pharmacokinetics
po	Oral
RD	Fraction of drug bound to the receptor
Rtot	Total concentration of receptors
sc	Subcutaneous
SEM	Standard error of the mean
ST	Single twitch stimulation
T1/2	Elimination rate constant half-life
$t_{1/2\beta}$	Elimination rate constant half-life
$T_{1/2}K_{eo}$	Equilibrium half-life between plasma concentration and effect
Tmax	Time at maximum plasma concentration
TOF	Train-of-four stimulation
Vdss	Apparent Volume of distribution at steady state

KEY WORDS

Pharmacokinetics

Pharmacodynamics

Neuromuscular blocking drugs

doxacurium

input rate

onset of action

intravenous

bolus

infusion

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My special thanks are extended to the committee members for taking the time out of their busy schedules to review this work and help me to complete my journey.

Most of all, I would like to thank my loving husband and my parents for their unconditional love, endless support, constant encouragement, and limitless confidence in my abilities. Without their assistance and continued support, I

would not have been able to complete this work. Although they may not have always understood what I was saying, they were always there to listen.

DEDICATION

This Thesis is dedicated to:

Professor France Varin.

Without her patience, encouragement and understanding, this work could not have been completed.

LITERATURE REVIEW

1. MECHANISM OF ACTION OF NEUROMUSCULAR BLOCKING DRUGS

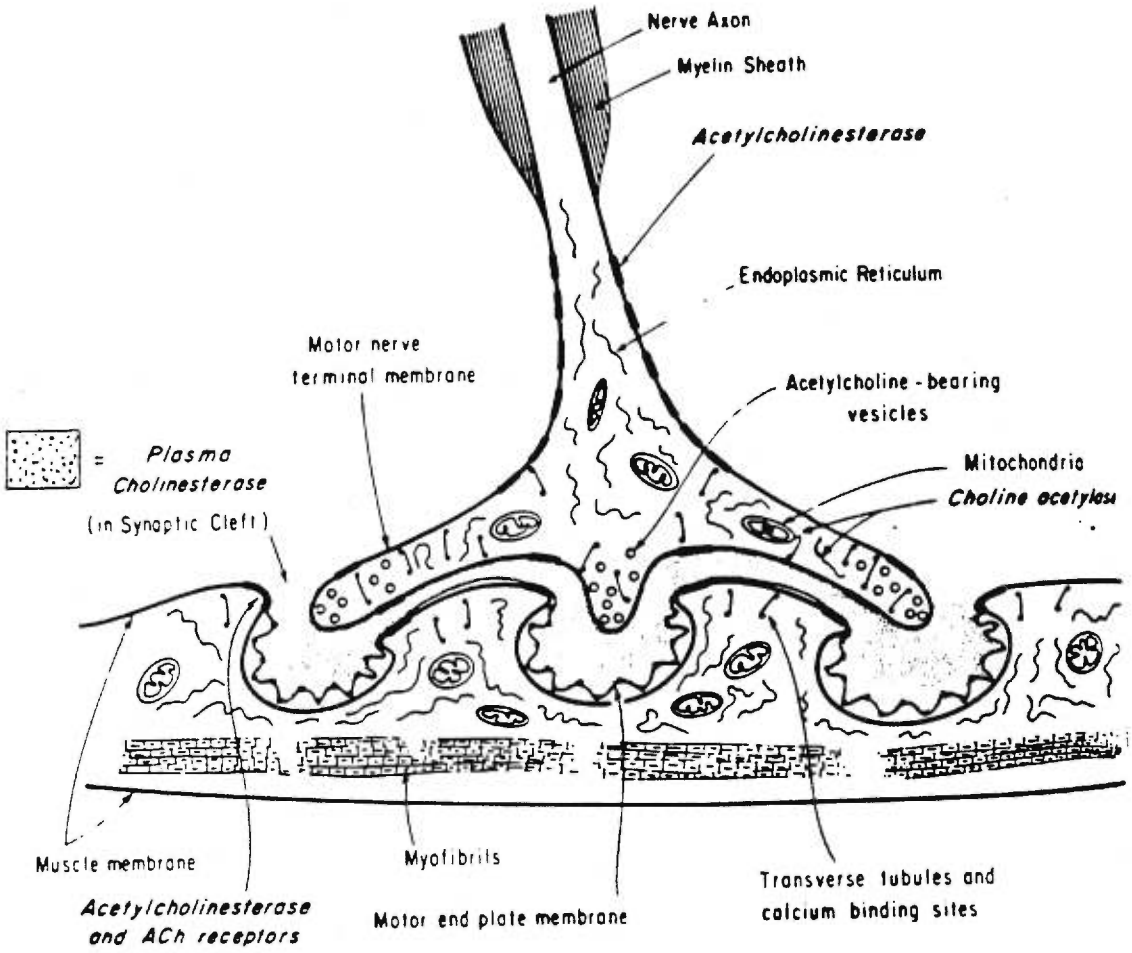
1.1 ANATOMY OF THE NEUROMUSCULAR JUNCTION (NMJ)

The fundamental anatomy of the frog NMJ was described by Birks et al. in 1960 (Birks et al, 1960), and serves as a model for other species. The NMJ consists of three parts: the motor nerve terminal, the synaptic cleft, and the motor end plate (Fig. 1). The nerve terminal contains not only mitochondria and other common subcellular structures, but also numerous vesicles about 70 nm in diameter. These vesicles have been shown to be filled with acetylcholine (ACh). Transverse bands can be seen on the motor nerve terminal membrane, and these have been called "active zones" because they were believed to be the sites of Ach release. There are about 1000 such active zones at each nerve ending (Ceccarelli and Hurlbut, 1980).

The junctional cleft is about 60 nm across and contains a basement membrane material that is a mucopolysaccharide. Acetylcholinesterase (AChE) exists within this basement membrane, although it is particularly concentrated in the folds of the motor end plate membrane (Hirokawa and Heuser, 1982). The Ach released from motor nerve terminal has to traverse the cleft before it reaches the receptors on the motor end plate membrane.

FIGURE 1

Schematic representation of neuromuscular junction



The NMJ consists of three parts: the motor nerve terminal, the synaptic cleft, and the motor end plate. The motor nerve terminal is nonmyelinated, and certain subcellular structures involved with energy production (mitochondria), protein synthesis, and acetylcholine synthesis and storage (endoplasmic reticulum and synaptic vesicles). The synaptic cleft is filled with extracellular fluid. The motor end plate is a uniquely chemosensitive, highly folded area of muscle membrane located opposite the motor nerve terminal. (adapted from Ali HH and Savarese JJ, 1976)

The motor end plate membrane is thrown into folds (secondary clefts), with the Ach receptors organized in discrete clusters located on the shoulders of those folds. This means that they are in direct apposition to the active zones of the nerve terminal (Daniels and Vogel, 1975). There are more than 10,000 receptors/μm^2, each of which is inserted through the phospholipid bilayer of the motor end plate membrane (Fig. 2).

On closer examination of motor endplate membrane nicotinic Ach receptor, it can be seen that it is a pentamer composed of five glycoprotein subunits, which together form a central cation channel (Fig. 2). Two of the subunits are designated α and have the same amino acid sequence. The others are known as the β, δ, and ε subunits in the mammalian adult and are about 40% identical in their amino acid sequences. Only the α subunits carry the primary recognition sites for the binding of ACh, other agonists, toxins (Lee, 1972), and reversible antagonists, such as nondepolarizing neuromuscular blocking drugs (Kistler et al, 1982; Peper et al, 1982; Stroud, 1983). Although the two α subunits have the same amino acid sequence, they reside in different environments. One α subunit has the β and the ε adjacent to it, whereas the other is surrounded by the δ and the ε subunits. This results in the properties of the two sites being different.

This channel is opened only when two Ach (or other agonist) molecules simultaneously attach to ACh binding sites on the α subunits, one on each, which causes the subunits to rotate into a conformation that opens the channel (Guy

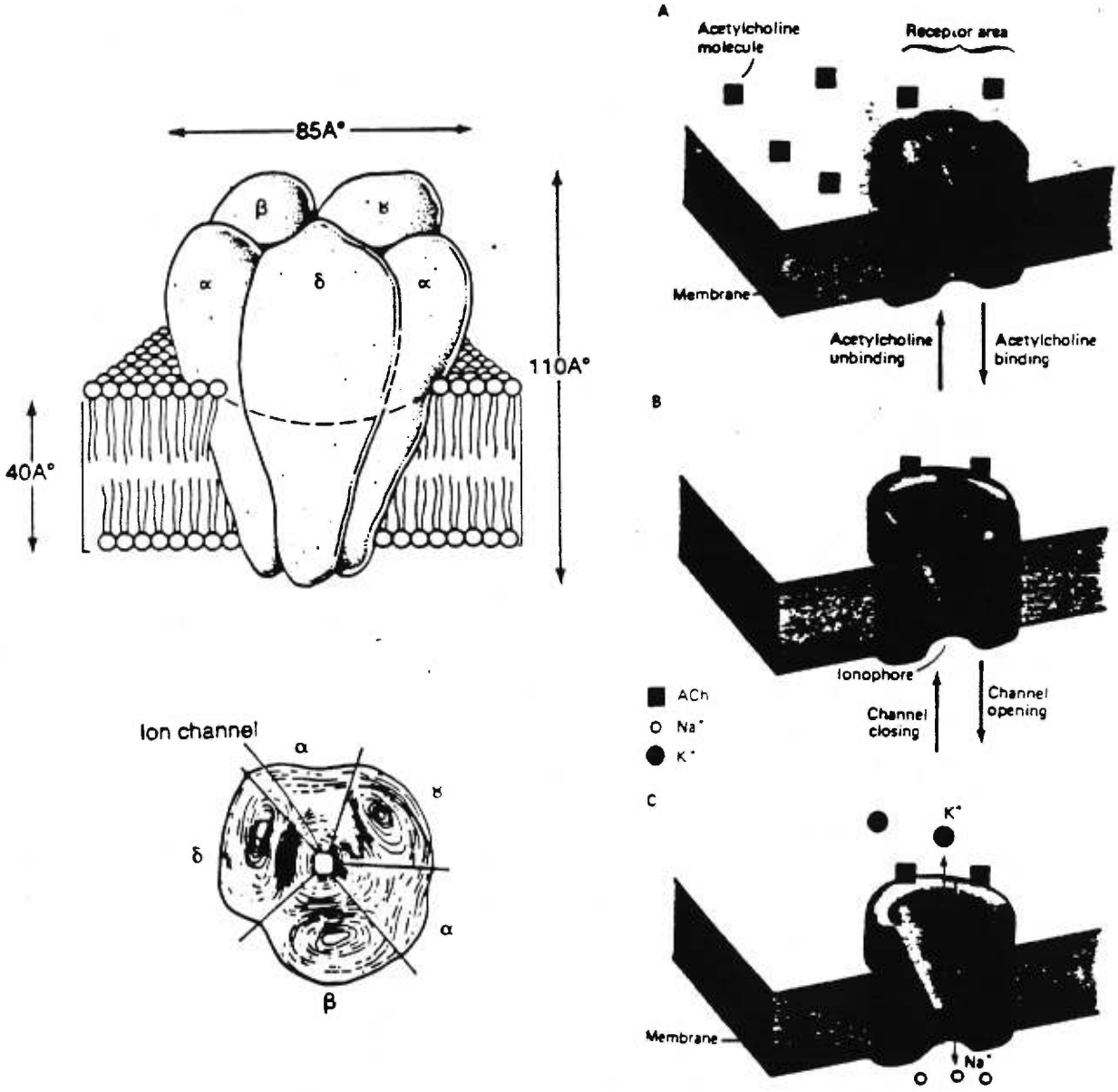
HR. 1984). When the channel is opened, sodium moves into while potassium moves out (Fig. 2). The neuromuscular nicotinic ACh receptor has been described as a ligand-gated ion channel because it consists of several subunits that are inserted into a membrane and provide ligand-gated conductance (Mishina et al, 1984, Changeux JP. 1990).

1.2 NEUROMUSCULAR TRANSMISSION (NMT) AND BLOCKADE

On the arrival of a nerve impulse, a burst of molecules of the neurotransmitter Ach is released from the motor nerve terminal. ACh crosses the junctional cleft and binds to the two α subunits in terminal endplate membrane nicotinic ACh receptor. This binding opens channels permeable to both sodium and potassium. The flow of these ions into and out of the cell depolarizes the cell membrane, providing the end-plate potential. This depolarization produced by the end-plate potential opens neighboring voltage-gated sodium channels to elicit a muscle action potential (MAP). Acetylcholine is then rapidly broken down by the enzyme acetylcholinesterase, which is present in the junctional cleft. Therefore, the depolarization caused by ACh is only for a short period of time. This allows the sodium channels to reset to their resting state before the next nerve impulse arrives and be ready to transmit another impulse. This neurotransmitter also stimulates the motor nerve terminal receptors to mobilize more acetylcholine for

FIGURE 2

The molecular structure of the Ach-activated receptor channel in human



The postjunctional nicotinic cholinergic receptor consists of five subunits (α, α, β, δ and γ. γ is the fetal form of ε unit) arranged to form an ion channel. When two ACh (or other agonist) molecules simultaneously attach to ACh binding sites on the α subunits, one on each, the channel opens, which allows Na+ and K+ move into and out of the cell, respectively. (adapted from Marshall and Waigh, 1994)

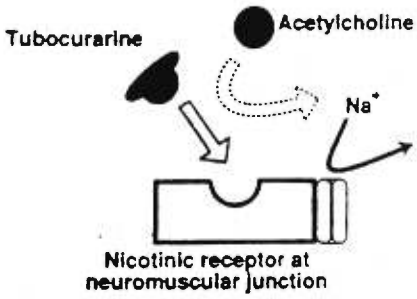
subsequent release from the nerve ending.

Neuromuscular transmission can be blocked by a substance (agonist and antagonist) that is able to bind to the ACh recognition site on one of the α subunits of the receptor. The binding of agonist or antagonist to the receptor will prevent ACh molecules from binding. Depending on the different mechanism of action of agonist and antagonist, the neuromuscular blockade falls into two categories: depolarizing neuromuscular blockade and nondepolarizing neuromuscular blockade.

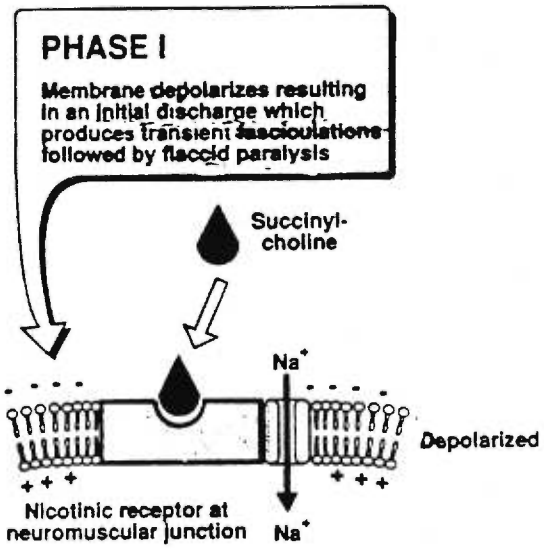
Depolarizing neuromuscular blockade is caused by agonist (depolarizing neuromuscular blocking agent, such as succinylcholine), which attaches to the nicotinic receptor, binds to the α subunits and acts like ACh to depolarize the junction (Fig. 3). Unlike ACh, which is instantly destroyed by AChE, the depolarizing agents are not susceptible to hydrolysis by the AChE. They persist at high concentrations in the synaptic cleft. They remain attached to the receptor for a relatively longer time, providing a constant stimulation of the receptor. The depolarizing agents first cause the sodium channel associated with the nicotinic receptors to open, which results in depolarization of the receptor (phase I). This causes a transient twitching of the muscle (fasciculations). The continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, the continuous depolarization gives way to gradual

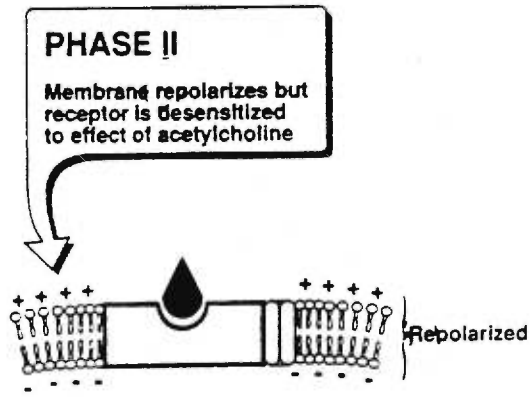
FIGURE 3

Mechanism of action of depolarizing and non-depolarizing neuromuscular blocking agents.



Mechanism of action of competitive neuromuscular blocking drugs.





Mechanism of action of depolarizing neuromuscular blocking drugs.

repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (phase II) and a flaccid paralysis.

Non-depolarizing neuromuscular blockade is caused by antagonist occupation (nondepolarizing neuromuscular blocking agents, such as doxacurium). The principal action of nondepolarizing agents is to prevent depolarization of endplate. Nondepolarizing agents can combine with the nicotinic receptor and prevent the binding of ACh (Fig. 3). The channel thus will not be opened, and the membrane will not be depolarized because no current will flow through it. Therefore, no end-plate potential is produced to open neighboring sodium channel to elicit a muscle action potential. This interaction between ACh and nondepolarizing agents is competitive, and a dynamic equilibrium exists, which favors either ACh or non-depolarizing agents depending on concentrations within the active biophase. In addition to these motor endplate effects, motor nerve terminal binding of nondepolarizing neuromuscular blocking drugs may oppose mobilization and release of ACh (Bowman et al, 1980, 1984).

1.3 THE SAFETY MARGIN OF NEUROMUSCULAR TRANSMISSION

The existence of a safety margin of neuromuscular transmission was firstly pointed out by Paton and Waud in 1967 (Paton & Waud, 1967), who reported the existence of high density of receptors at the neuromuscular junction. Neuromuscular blockade is not manifested until a large proportion of receptors is

occupied. After that, Waud and Lee demonstrated that more than 75% of receptors must be occupied before a significant depression of evoked muscle responses can be observed. Once the safety margin is overcome, there is only a narrow range of receptor occupancy (75%-92%) over which detectable changes in evoked muscle responses occur (Waud & Waud, 1972a; 1972b; Lee 1975) (Fig. 4). This process would take less time.

Based on the receptor occupancy theory, the "priming technique" was proposed to accelerate the speed of onset of nondepolarizing neuromuscular blocking drugs (Gergis et al, 1983, Foldes et al, 1984). The technique consists of the administration of a subparalysing dose of the drug before the remainder of the intended dose is given. The subparalysing or "priming" dose is thought to occupy a proportion of nicotinic receptors, thereby reducing the safety margin of the neuromuscular transmission before the injection of the intubating dose several minutes later. Since part of the critical number of receptors required for neuromuscular blockade are already occupied, subsequent increments only need to supplement for unsaturated receptors. Thus, the onset of action of the paralysing dose is more rapid (Donati & Meistelman, 1991; Feldman & Faurel, 1994) (Fig. 5).

1.4 MONITORING OF NEUROMUSCULAR FUNCTION

The response to neuromuscular blocking drugs is quite variable and unpredictable in the population at large (Katz, 1967; Silverman et al, 1992). This is more so in situations where the response to this class of drugs may be adversely modified by perioperative medication and/or disease states (Grob & Namba, 1976; Mitchell et al, 1978; Martyn et al, 1980; Feldman, 1963). Thus, to minimize patient morbidity, maximize patient comfort, and optimize surgical care, monitoring of neuromuscular block during the perioperative period is essential. The first order of importance in monitoring neuromuscular function is to titrate precisely individual dosage requirements of neuromuscular blocking drugs to provide adequate clinical relaxation. Determination of the optimal time for reversal and the prediction of the adequacy of recovery is another concern. Adequate muscle recovery can be more accurately assessed and correlated with other criteria of safe and optimum clinical recovery.

Neuromuscular function can be monitored by stimulating an accessible peripheral motor never and measuring the evoked response of the skeletal muscle supplied by that nerve. The choice of the neurostimulating site depends on several factors. However, in the practical sense accessibility to the superficial never intraoperatively is the most important. Essentially any superficial peripheral nerve may be stimulated. Measurement of the adductor pollicis response to ulnar nerve stimulation is most commonly used to monitor neuromuscular blockade (Fig. 6) because the ulnar nerve can be identified so readily. The greatest advantage in the use of the adductor pollicis is that under appropriate conditions,

it is the only muscle acting on the thumb (Merton, 1954) supplied by the ulnar nerve, and hence it approaches the single-muscle precision of the experimental nerve-muscle preparation. Also, this site is well suited for visual, tactile, and mechanomyographic assessments. Another advantage is that this muscle is on the lateral side of the arm, whereas the site of stimulation is on the medial side; therefore, there is little chance of direct muscle stimulation, which might distort assessment.

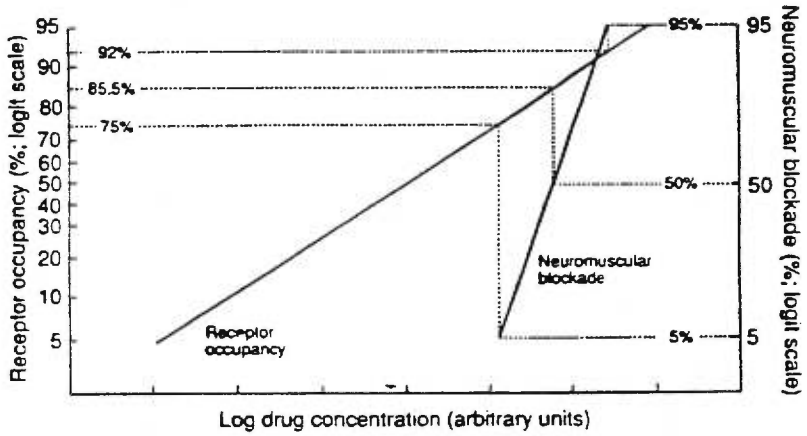
There are many available patterns of neurostimulation, such as single twitch, train-of-four (TOF), double burst (DBS) and tetanic stimulation. The selection of patterns of nerve stimulation depends on the particular clinical setting.

1.4.1 Train-of-four (TOF) Stimulation

TOF pattern has been in use since the early 1970s (Ali et al, 1970) and has become the standard method of assessing neuromuscular block in clinical practice. TOF stimulation utilizes simple short train of stimuli at a frequency of 2 Hz for a duration of 2 seconds (i.e., one stimulus every 0.5 second). When used continuously, each set (train) of stimuli normally is repeated every 10th to 12th seconds (Fig. 7). Each stimulus in the train causes the muscle to contract, and "fade" in the response provides the basis for evaluation. That is dividing the amplitude of the fourth response by the amplitude of the first response provides the TOF ratio. In the control response (the response obtained just before

FIGURE 4

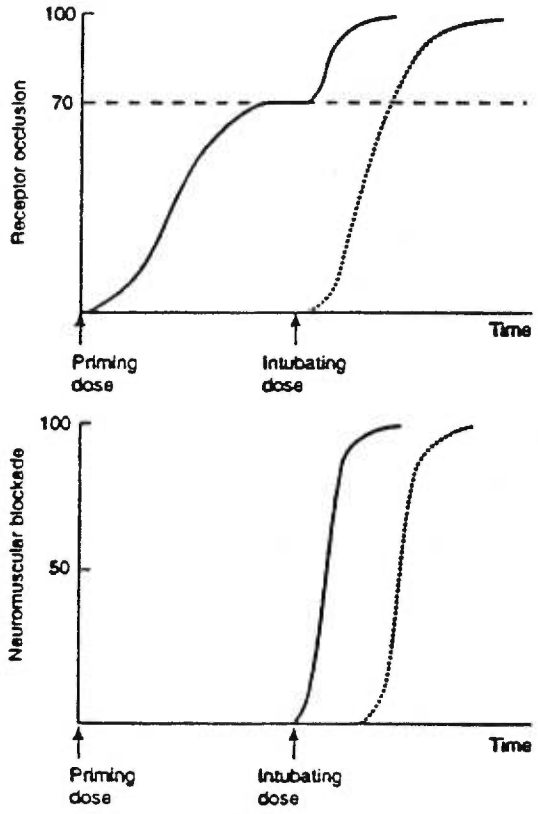
Relationship between receptor occupancy, neuromuscular blockade and drug concentration



Neuromuscular blockade occurs over a narrow range of receptor occupancy. At 75% receptor occupancy, blockade is only 5%. Blockade is 95% complete at 92% receptor occupancy (adapted from Donati and Meistelman, 1991)

FIGURE 5

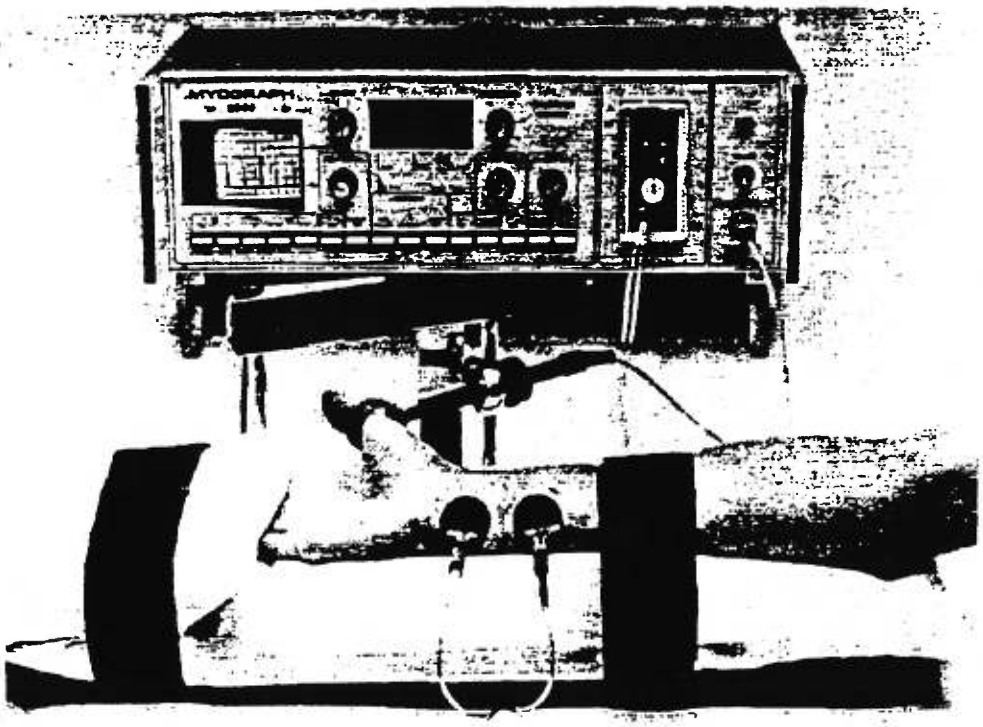
The theoretical representation of priming



The lower trace shows the increased neuromuscular block and the upper trace the receptor occupancy. The administration of a priming dose occupies just less than 70% of the receptors, but there is no effect on transmission. The intubating dose only has to increase receptor occupancy from 70% to 100% and so, onset is rapid. When an intubating dose is given without priming (dotted lines), there is a delay until receptor occupancy has exceeded 70% before neuromuscular block begins. (adapted from Feldman and Fauvel, 1994)

FIGURE 6

Photograph of monitoring of neuromuscular function.



The hand and forearm immobilized for recording thumb adduction in a special arm board. Stimulating electrodes are placed on the surface of the skin or percutaneously along the ulnar nerve at either the wrist or the elbow. The evoked tension of the adductor pollicis in response to ulnar nerve stimulation is recorded using a force-displacement transducer. (adapted from Vibi-Mogensen, 1983)

administration of neuromuscular blocking drug), all four responses are ideally the same: the TOF ratio is 1.0.

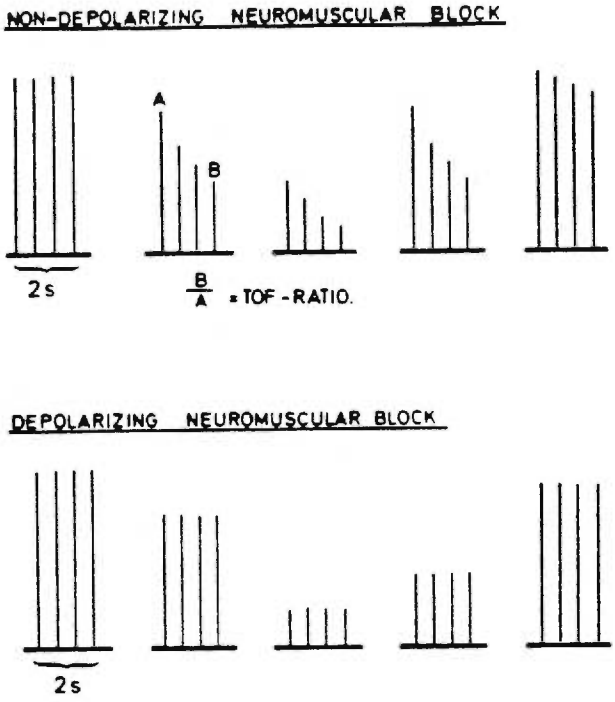
During a partial nondepolarizing blockade, this frequency is associated with clearly separated muscle responses that exhibit a progressive decrease in amplitude and the ratio decreases (fades)(Fig. 7). The degree of fade is inversely proportional to the degree of blockade. Thus, the TOF ratio estimates the extent of nondepolarizing blockade. In a partial nondepolarizing blockade, the T4 amplitude starts to decrease when 70% to 75% of the receptors are occupied, whereas the T1 response may not decrease until the T4/T1 ratio decreases below a value of 0.7. When the T4 response is lost completely, approximately 80% of the receptors are blocked. Disappearance of the third (T3) and second (T2) responses corresponds to 85% and 85% to 90% of receptor occupancy, respectively (Lee C, 1975). When 90% to 95% of the receptors are blocked, T1 disappears, its amplitude decreasing progressively with increasing receptor occupancy (Waud et al, 1972, Lee C, 1975,). The recovery of these responses occurs in the reverse order.

During a partial depolarizing blockade, the twitch height is reduced to the same extent in all four responses, no fade occurs in the TOF response; ideally, the TOF ratio is approximately 1.0 (Fig. 7). Fade in the TOF response after injection of succinylcholine signifies the development of phase II block.

The advantages of TOF stimulation are greatest during nondepolarizing blockade, as the degree of blockade can be read directly from the TOF response, even though a preoperative value is lacking (Ali et al, 1970; Lee C, 1975; Ali et al, 1981). In addition, TOF stimulation has some advantage over tetanic stimulation, as the former is less painful and, unlike tetanic stimulation, generally does not affect the degree of neuromuscular blockade. However, following the injection of succinylcholine and atracurium, the onset and recovery of neuromuscular blockade monitored by using 0.08 Hz single-twitch stimulation were found to be different from those with TOF stimulation. Although these differences were statistically significant, they were too small to be clinically important (Curran et al, 1987).

FIGURE 7

Pattern of electrical stimulation and evoked muscle responses to TOF nerve stimulation



Four equal muscle contractions (twitches) are produced in the absence of muscle relaxation; reduction in twitch height indicates the depth of neuromuscular blockade.The train-of-four ratio (B/A) becomes less than 1 only in the presence of nondepolarizing neuromuscular blockade (adapted from Viby-Mogense, 1989).

2. FACTORS AFFECTING THE ONSET OF NEUROMUSCULAR BLOCKADE

The onset time is defined as the period between administration of the drug and maximal effect. In studies of neuromuscular blocking drugs relaxation is usually assessed with ulnar nerve stimulation and measurement of force generated by the adductor pollicis.

Neuromuscular blocking drugs are important adjuvants to general anaesthetic agents. One of their major uses is to facilitate endotracheal intubation and secure the patient's airway during surgery. To ensure suitable conditions for intubation, a neuromuscular blocking drug should produce a maximal effect as rapidly as possible after its intravenous administration, ideally within 60 to 90 seconds (Jones et al, 1984). This delay of action is critical to avoid pulmonary aspiration of gastric contents. However, the degree of paralysis required for easy laryngoscopy and tracheal intubation is not achieved immediately after the injection of neuromuscular blocking drugs.

Succinylcholine is the neuromuscular blocking drug with the fastest onset. Doses of 1-1.5 mg/kg provide excellent intubating conditions in 60 to 90 seconds (Miller & Way, 1971; Cullen DJ, 1971; Blackburn & Morgan, 1978; Ferguson & Bevan, 1981; Blitt et al, 1981; Geris et al, 1983; Manchicanti et al, 1985). It is, therefore, the drug of choice when it is necessary to secure the airway as rapidly as

possible (rapid sequence induction of anaesthesia). Unfortunately, succinylcholine is a depolarizing neuromuscular blocking drug which is contraindicated in certain patients and has annoying side effects in most others (Durant & Katz, 1982; Donati & Bevan, 1985). Although significant improvements have been made with the introduction of nondepolarizing neuromuscular blocking drugs, for most of them, there is a delay in onset of action, and complete muscle relaxation is observed only after 5 to 7 minutes (Uting et al, 1982). Thus it is very important to determine the factors which modify the onset of action of neuromuscular blocking drugs in order to achieve the shortest time possible in clinical practice.

Generally, onset depends on the arrival at the receptor of sufficient molecules either to produce depolarization of the endplate (depolarizing neuromuscular blocking drugs) or to prevent acetylcholine from reaching enough receptors to cause neuromuscular transmission (nondepolarizing neuromuscular blocking drugs). Speed of onset is affected mainly by the rate of delivery of the drug to the junction. It is modified by the dose, drug potency, physico-chemical properties and its disposition in plasma. To understand this, one must consider that the intravenously injected drug must reach the target organ, diffuse from the intravascular space to the site of action, and interact with the receptor before it is taken away from the neuromuscular junction. The neuromuscular junction concentration, not plasma concentration, is the key factor in determining onset of action. Furthermore, certain patients characteristics are likely to affect the onset

of action, either because potency is altered, or because the factors which affect delivery to, and removal from the neuromuscular junction are altered.

2.1 DELIVERY

Neuromuscular blocking drugs are usually injected into a peripheral vein, and carried to their site of action via the blood stream. Thus, the time from administration of drug and its effect is modified markedly by circulatory factors.

2.1.1 Cardiac output

After intravenous injection, the drug is carried to the central circulation where it mixes with venous blood coming from all organs. Then it enters the right ventricle side of the heart, goes through the pulmonary circulation and the left ventricule to the aorta. The transition time from peripheral venous to arterial circulation depends on cardiac output. This factor has been identified as a major factor affecting succinylcholine onset (Harrison & Junius, 1972). The onset time of non-depolarizing neuromuscular blocking drug was found to be shorter in infants, who have a relatively large cardiac output, compared to older children (Bevan et al, 1985; Smith et al, 1987). Within the adult population, the speed of action of pancuronium is shown to be slower in the elderly than younger subjects, and this was attributed to the decreased cardiac output in the elderly (Donati & Bevan, 1986).

2.1.2 Circulation time to muscle

Before the drug reaches the muscle, the drug-containing blood which first appears in the aorta must push the drug-free blood ahead of it in the arteries and capillaries. The time involved in this process will depend on the volume of blood contained in the blood vessels concerned and how quickly it circulates. That is, on the distance to the target organ and its blood flow. It follows that the muscle which are closer to the central circulation and have a better perfusion tend to be paralyzed more rapidly than more peripheral, less perfused muscles. For example, when full therapeutic dose is given, meuromuscular blockade was found to occur earlier at the diaphragm (Charvin et al, 1987; Pansard et al, 1987; Donati et al, 1990) and vocal cord (Donati et al, 1991) muscle than adductor pollicis muscle. The data were explained by the higher blood perfusion of these muscles, compared with peripheral muscle (Brancatisano et al, 1993).

2.1.3 Muscle blood flow

When the neuromuscular blocking drug firstly reaches the neuromuscular junction area, there is a high concentration gradient between the blood and surrounding tissue. Thus, a large proportion of the drug will diffuse out of the intravascular space into the tissue. The time to reach a given drug concentration

at the receptor site then depends on how quickly fresh drug arrives, that is on muscle blood flow.

Muscle perfusion has the greatest potential to be affected by altered pathophysiology. Many experiments have been designed to show that muscle blood flow, or factors that may indirectly alter muscle blood flow, do affect onset time for neuromuscular blocking drugs. Enhanced muscle blood flow accelerates the onset of paralysis, while decreased muscle perfusion delays the onset of paralysis.

In dogs, the onset time of gallamine neuromuscular blockade in the tibialis anterior muscle was found to be shortened by increasing blood flow to the muscle (Goat et al, 1976). A delayed onset of paralysis has been determined in patients having a moderate degree of hypothermia, presumably due to decreased muscle perfusion (Ham et al, 1981). A recent study with doxacurium demonstrated a decrease in onset time for maximum blockade in the elderly, which was attributed to an age-related reduction in muscle blood flow (Gariepy et al, 1993).

Attempts to alter muscle blood flow in humans also have resulted in altered onset time. For example, with train-of-four stimulation in one arm, the onset time was found to be shorter for both atracurium and succinylcholine than that with single-twitch stimulation in the contralateral arm (Curran et al, 1987). The explanation

was that continued train-of-four stimulation increased local blood flow because of increased oxygen requirements for the contracting muscle, and this increase was greater than with single-twitch stimulation.

2.2 TRANSFER

2.2.1 Input rate into biophase

Onset of action does not occur immediately after injection of the neuromuscular blocking agent (Table 1). This discrepancy between drug plasma concentration and effect has been explained satisfactorily by a hypothetized effect compartment (biophase) (Segre, 1968; Hull et al, 1978; Sheiner et al, 1979), in which drug concentrations would be directly related to effect. Maximum effect occurs when drug plasma concentration equilibrate with drug concentration at effect site. Some time is needed before a sufficient number of drug molecules reach the neuromuscular junction and equilibrate with plasma. An index of this equilibrium time delay is expressed by the rate constant, Keo. This rate constant is a measurement of accessibility of drug to its effect site, and indicates its transfer rate from central compartment (blood) to effect compartment. Therefore, faster equilibrium is expected to be associated with rapid onset.

Table 1. Potency, onset and duration of action of neuromuscular blocking drugs.

Drug	ED_{95} Under N_2O/O_2 (mg/kg)	Potency factor	$2XED_{95}$ Dose Onset time[a] (min)	Clinical duration[b] (min)
Long-acting				
Pancuronium	0.07	1	3-6	60-120
Metocurine	0.28	4	3-6	60-120
d-Tubocurarine	0.5	7	3-6	60-100
Gallamine	3.0	40	3-6	90-120
Alcuronium	0.25	9	3-6	60-120
Doxacurium	0.025	0.4	4-6	90-120
Pipecuronium	0.05	0.8	2-4	80-110
Intermediate-acting				
Vecuronium	0.05	0.8	2-4	45-90
Atracurium	0.23	3.5	2-4	30-45
51W89	0.05	1	2-3	40-75
Rocuronium	0.3	6	1.5-3	45-75
Short-acting				
Mivacurium	0.08	1.6	2-3	15-20

a: The time from injection to the maximum blockade
b: The time to 25% recovery

Several factors affect the Keo value. These include muscle perfusion (e.g. blood flow), drug diffusibility from the capillary lumen to the biophase (e.g. molecular weight, Pka, lipid solubility), drug blood : muscle partitioning (e.g. plasma protein binding and non-specific tissue binding), and receptor events (Hennis & Stanski, 1985). Of these factors, muscle perfusion and drug muscle:blood solubility play major role in determination of Keo value. Sheiner et al (1979) found a t1/2Keo of 5 minutes for d-tubocurarine, which was not markedly different from a theoretical value that would only take into consideration muscle perfusion and the drug muscle:blood partition coefficient. They therefore concluded that these two factors were the rate-limiting steps to Keo. Gariepy et al (1993) reported the prolonged t1/2Keo of doxacurium in aged people, presumably because of a decreased muscle blood flow. A recent study shows that by using the "priming technique" to occupy the critical number of receptors to overcome the safety margin of neuromuscular transmission, the significantly decreased onset time of atracurium was not associated with a faster Keo, which in fact remained unchanged. This study showed that receptor events are not a limiting factor for Keo. The Keo value would take into account mainly pharmacokinetic factors, such as muscle blood flow, drug diffusibility and the drug muscle:blood partition coefficient (Ducharme et al, 1995). High tissular perfusion and low tissue : blood partitioning were expected to be associated with higher Keo value (Donati, 1994).

Keo values range from 4 to 13 minutes for neuromuscular blocking agents. These variations were attributed to methodological factors, such as sampling

site: venous vs arterial blood (Donati et al, 1991; Mastey et al, 1995); sampling schedule: rapid sampling vs traditional sampling (Ducharme et al, 1993; Mastey et al, 1995); anaesthesia procedure: previous administration of succinylcholine (Donati et al, 1991); and different type of intravenous administration: bolus vs infusion (Ducharme et al, 1994).

2.2.2 Lipophilicity

Lipophilicity plays an important role in the speed of onset of neuromuscular blocking drugs. Increase in lipophilicity is associated with an increase in the unbound clearance, which causes an increase in total plasma clearance (Wierda & Proost, 1995). Meanwhile, increased lipophilicity coincides also with a higher rate of drug transport from plasma to the biophase (Keo) (Wierda & Proost, 1995). Both rapid elimination of drug from plasma and fast transfer of drug from plasma to biophase will lead to a shortening on onset time. Wierda & Proost (1995) investigated the relationship between lipophilicity and onset time of steroidal neuromuscular blocking drugs, and concluded that changes in the molecular structure of steroidal neuromuscular blocking drugs which enhance the lipophilicity, coincide with a decrease in onset time (Table 2).

Table 2. Physico-chemical characteristics and pharmacodynamic parameters of six steroidal neuromuscular blocking drugs

	Rocuronium	Vecuronium	Org 9489	Org 9487	Org 9453	Org 7617
Protein bound fraction	0.25	0.57	0.63	0.62	0.72	0.72
Octanol/Kreb partition coefficient (P)	0.16	0.17	0.78	1.05	2.70	3.65
Onset time (min)	3.60	5.00	3.00	2.10	1.70	1.20
ED_{90} (mg/kg)	0.30	0.05	0.45	1.00	1.20	3.70

2.2.3 Plasma protein binding

Neuromuscular blocking drugs are ionized, water soluble basic compounds. The plasma proteins mainly involved in the binding of basic drugs are albumin, α1-acid glycoproteins and lipoproteins. Once the neuromuscular blocking drug binds to these plasma proteins, it becomes "unavailable" to induce a neuromuscular blockade because only the unbound drug can cross cell membranes, reaches the postsynaptic membrane at the neuromuscular junction, and binds to Ach receptors to produce neuromuscular blockade. A lower fraction of free drugs in plasma will lead to fewer drug molecules being delivered to the neuromuscular junction per unit time. Therefore, longer time is needed to occupy the critical number of receptors to elicite neuromuscular blockade.

2.2.4 Diffusion of drug from the capillary lumen to the biophase

After the neuromuscular blocking drug reaches the extracellular fluid of the muscle, it must gain access to the biophase. This procedure occurs by drug diffusing out of the capillary lumen into the muscular interstitial fluid where it will act. If physicochemical factors (ionization, molecular size) significantly limit the rate of diffusion into the biophase, this can be translated into a delayed onset.

2.2.5 Biophase binding

Once the drug has reached the biophase, several processes can occur. The drug can reach the receptor sites within the biophase and induces the drug effect. The drug can also bind nonspecifically to various (nonreceptor) proteins within the biophase analogous to the drug-protein binding that occurs in blood. If the drug is bound to proteins that are not relevant in creating the drug effect, the drug is effectively "unavailable" to induce a pharmacological effect. An indirect measure of these processes is the drug non-specific tissue binding. A relatively high binding of the drug in a tissue suggests high "nonspecific tissue binding" such that the rate of equilibration between blood and tissue of the pharmacologically active concentrations will be prolonged. The onset time will be therefore increased. This explains also the difference between pharmacological and biological half-lives.

2.3 RECEPTOR EVENTS

2.3.1 Rate of binding

Once present in the synaptic cleft, the rate of binding of drug molecules to the acetylcholine receptor is extremely rapid and the delay between binding and pharmacological effect is very short (Armstrong & Lester, 1979). D-tubocurarine molecules have been shown to move into and leave out of the synaptic area in a few milliseconds (Eccles & Jaeger, 1958). Therefore, this last process is not expected to contribute significantly to onset time. Thus, these interactions at the molecular level are not expected to affect onset time.

2.3.2 Tissue responsiveness (Sensitivity)

Muscle groups differ in their sensitivity to neuromuscular blocking drugs (Johansen et al, 1964). The exact cause of these differences is multifactorial and may include variable regional blood flow among muscle groups, differences in muscle temperature, differences in the density of receptors, varying margins of safety at the neuromuscular junction among muscles, and differences in muscle fiber composition (Brull, 1994). Compared with the adductor pollicis muscle, the diaphragm is relatively more resistant to depolarizing and non-depolarizing neuromuscular blocking drugs and requires twice the amount of drug to achieve the same degree of neuromuscular blockade (Smith et al, 1988; Donati et al, 1986). When full therapeutic doses of neuromuscular blocking drugs are used, the faster onset time at the diaphragm tends to predominate, and adequate diaphragmatic blockade is evident before adductor pollicis muscle block because of the higher regional blood flow in diaphragm (Donati et al, 1990). However, if lower doses are used, the lesser sensitivity of the diaphragm may predominate, and the adductor pollicis evoked responses are ablated 30 to 60 seconds before maximal diaphragmatic blockade.

Just as the administered dose can change the apparent onset of paralysis, so can a change in the tissue responsiveness alter the onset of paralysis. If the patient is "sensitive", then the onset of paralysis will appear more rapidly because

in the sensitive patient, a smaller amount of drug is needed at the neuromuscular junction to achieve the same degree of paralysis. For a given dose of neuromuscular blcoking drug, this amount of drug will be achieved at an earlier point in time after the iv bolus injection.

Examples of an increased sensitivity are found in myasthenia gravis patients, and when nondepolarizing neuromuscular blocking drugs are administered concomitantly with inhalational anesthestic agents, such as halothane (Stanski et al, 1979). The opposite occurs if the patient is "resistant". An example of resistance occurs in patients with thermal burns.

2.4 DOSE

Clinically, neuromuscular blocking drug is not usually administered as its ED95 dose, but as a dose of about two to three times of the ED95. Larger doses cause higher peak blood concentrations, which result in more drug being delivered to the neuromuscular junction in the first few circulation times. The larger amount of drug delivered to the neuromuscular junction causes the most rapid onset of paralysis (Healy et al, 1986). Increasing the dose shortens the delay between injection and the time when the concentration of drug at the neuromuscular junction exceeds that necessary to produce 100 per cent blockade. Therefore, time to maximum blockade decreases markedly with dose in the one to three times ED95 range. However, at doses greater than three times ED95, the time to

100 per cent blockade does not decrease markedly with increasing dose. Thus, at high doses, the limiting factor appears to be the time required for the drug to reach the neuromuscular junction, which in turn, depends on circulatory factors, such as cardiac output, the distance of the muscle from the central circulation, and muscle blood flow.

2.5 POTENCY

There is considerable evidence that a potent drug has a slower onset of action than a less potent drug. In the cat, Bowman et al found an inverse relationship between time to maximum blockade and the effective dose for 50% blockade (ED50, potency), and suggested that, for a series of steroidal muscle relaxants, onset time decreased as ED50 increased (Bowman et al, 1988). In humans, Kopman found that when equipotent doses of gallamine, d-tubocurarine, and pancuronium were administered, maximum blockade was identical for all three drugs, but blockade developed more slowly with the more potent pancuronium, and more rapidly with the less potent gallamine (Kopman, 1989). This inverse relationship between speed of onset and drug potency was also demonstrated in vitro by iontophoretic application of neuromuscular blocking drugs to the neuromuscular junction area, where onset time inversely correlated with potency (Law-Min et al, 1992).

To account for these experimental data showing decreased speed of onset with increased potency of neuromuscular blocking drugs, Donati and Meistelman (1991) postulated, on theoretical ground, that if equipotent doses are given, drugs with low potency might have a faster onset of action than those with higher potency do. A pharmacokinetic-pharmacodynamic model characterized by a finite concentration of receptors in the effect compartment was presented to explain the relationship between high potency and slow onset of action for neuromuscular blocking drugs. The principle of this model is that neuromuscular junction can be regarded as a dense cluster of receptors, and no matter the potency of the neuromuscular blocking drug, a large proportion of receptors (more than 90%) must be occupied before neuromuscular blockade is manifested (Paton & Waud, 1967). Since effect depends on the presence of a critical number of drug molecules at the site of action, no effect can be observed until this number of molecules has reached the receptor area. It follows that if the drug is potent, i.e., if a small dose has been given, fewer molecules are delivered to the neuromuscular junction per unit time. Thus, this critical number will be carried into a longer time period.

Doxacurium is the most potent neuromuscular blocking drug available at present time, and it has the longest onset times. Subparalyzing doses reach maximum blockade within 10 to 15 minutes.

2.6 DRUG DISPOSITION IN PLASMA

As mentioned above, maximum effect occurs when the blood concentration equilibrates with the drug concentration at effect site, and this equilibrium is attained rapidly if the factors which promote access to the neuromuscular junction are favorable. It also occurs early if the blood concentration of the drug decrease rapidly.

It is well known that the rapid onset of succinylcholine is related to its rapid rate of metabolism. In patients with normal plasma cholinesterases, hydrolysis of succinylcholine is rapid and subparalyzing doses of succinylcholine produce their maximum effect within 1.5 - 2 minutes at the adductor pollicis (Smith et al, 1988; Szalados et al, 1990). In patients with little or no plasma cholinesterase activity, administration of a subparalyzing dose is associated with an onset time of 5 to 6 minutes, comparable to non-depolarizing neuromuscular blocking drugs (Hickey et al, 1987). This suggests that the rapid onset of succinylcholine in normal patients is not due to its mechanism of action at the neuromuscular junction, but to its rapid metabolism. For long and intermediate acting nondepolarizing neuromuscular blocking drugs, elimination processes are too slow to affect onset times significantly, thus, speed of onset is determined to a large extent by their distribution processes which occur at approximately the same rate because of their similarities in chemical structure, ionization and molecular weight. As a result, onset times for intermediate and long-acting neuromuscular blocking drugs are remarkably similar and rang between 5 to 7 minutes (table 2).

This raises the question of why mivacurium, which is a non-depolarizing drug whose active isomers have a half-life of 2 minutes (Lien, 1992), has onset times approaching 5 minutes or more (Savarese et al, 1988; From et al, 1990). The probable answer is that mivacurium is a very potent drug with a ED95 of 0.08 mg/kg (Table 1), and potent drugs tend to have slow onset time. This effect compensates for the rapid elimination rate of the drug.

3. DOXACURIUM

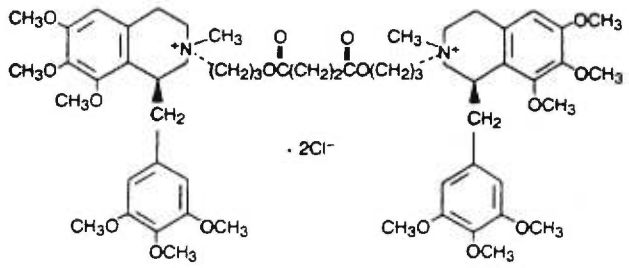
3.1 CHEMICAL STRUCTURE

Doxacurium is a bisquaternary benzylisoquinolinium diester. It contains two positive charges, which are separated by a bridging structure that is lipophilic (Fig. 8). The bridging structure is different for various series of neuromuscular blocking drugs and is a major determinant of potency (Miller, 1994). Positive charges in the molecule mimic the quaternary nitrogen atom of the transmitter Ach and is the principal reason for the attraction of the drug to cholinergic receptors. Doxacurium is highly water soluble. Its hydrophilic nature is mostly due to positive charges, which give doxacurium the physicochemical properties of cations in watery media such as the plasma and urine. Other chemical features of this drug that promote either water solubility or hydrophilic properties or both are methoxy groups in the molecule.

Doxacurium is a very potent long-acting benzylisoquinolinium ester with an estimated ED95 of approximately 30 µg/kg (Basta et al, 1988; Maddineni, 1992). Interestingly, although it is an ester of succinic acid, it undergoes no hydrolysis by pseudocholinesterases (Basta et al, 1988). It was introduced in 1991 as the first benzylisoquinolinium relaxant free of side effects (Basta et al, 1988; Reich et al, 1990). It is about 20 times as potent as d-tubocurarine and is indicated for longer operations (more than 3 to 4 hours) in which cardiovascular stability is

FIGURE 8

Chemical structure of the long-acting, nondepolarizing neuromuscular blocking agent: doxacurium chloride



Doxacurium chloride

important and in which early extubation is unnecessary. Therefore, it was developed as a potential long action alternative to pancuronium, metocurine, d-tubocurarine and alcuronium. Its commercial name is Neuromax® (Glaxo Wellcome Co.).

3.2 PHARMACOKINETICS

3.2.1 Absorption

Doxacurium is an ionized compound with two positive charges (Fig. 8). It can not be absorbed through gastro-intestinal tract and has to be administered intravenously.

3.2.2 Distribution

The pharmacokinetics of doxacurium has been described by compartmental (2- or 3- compartments) and noncompartmental analysis. The high water solubility of doxacurium generally prevents passage across lipoid membranous barriers, such as the blood-brain and placental barriers, and the lipid membranes of most cells, such as renal tubular cells, hepatocytes, and nerve and muscle cells. This is reflected by its small volume of distribution (Table 3). After initial redistribution, it is largely confined to the extracellular fluid compartment. In normal patients, the volume of distribution at steady state (Vdss) has been reported to vary from 0.12

to 0.23 L/kg for doses ranging from 15 to 80 μg/kg (DeAngelis et al, 1990; Dresner et al, 1990; Cook et al, 1991; Gariepy et al, 1993; Zhu et al, 1996). The small Vdss of doxacurium is consistent with the physicochemical properties of this large, polar compound with a molecular weight of over 1100 daltons.

The change of Vdss in the elderly varies from study to study. Dresner et al (1990) reported that the Vdss was significantly increased in the elderly and this change was attributed to the differences in initial fluid volume status, intraoperative blood loss, fluid replacement, and protein binding between the young and the elderly patients. However, Gariepy et al (1993) showed that Vdss was not altered by age, which is consistent with the fact that the volume of extracellular compartment is unchanged in the elderly (Rossman, 1979). Dresner et al (1990) attributed the increased Vdss to experimental factors because the only plausible change would be a decrease in Vdss.

In vitro studies showed that doxacurium is not exhaustively bound to plasma proteins, its plasma protein binding was approximately 30% in human plasma (DeAngelis et al, 1990). In young, elderly, and obese patients, the plasma protein binding of doxacurium was shown to be 47%, 50%, and 47%, respectively (Cameron et al, 1995).

3.2.3 Elimination

Though the disposition of doxacurium in human has not been fully characterized, preliminary studies indicate that it would be excreted by way of both urinary and biliary pathways (Dresner et al, 1990; Cook et al, 1991; Cashman et al, 1990; Gariepy et al, 1993) Renal excretion of unchanged drug appears to be an important elimination route for doxacurium, accounting for 16% to 31% of the dose (Table 3). Patients with renal dysfunction tend to clear doxacurium at a significantly slower rate than normal patients do (Cook et al, 1991). However, a non-negligible proportion of doxacurium may also be excreted through a hepatic pathway. It is reported that biliary concentrations of doxacurium were 13 to 445 times higher than the plasma concentrations in five patients undergoing cholecystectomy (Dresner et al, 1990). Patients with hepatic failure tend to clear doxacurium at a slower rate than normal patients do, eventhough it is not significant. Thus biliary excretion may also play a role in the elimination of doxacurium.

Finally, in vitro data have shown doxacurium to be a weak substrate for plasma cholinesterase (Basta et al, 1988). When enzyme-catalyzed rate of hydrolysis by human cholinesterases was estimated at high substrate concentrations, the hydrolysis rate of doxacurium in vitro was 0.16 ± 0.01 μM/h, or approximately 6% of the rate of succinylcholine. Therefore, its contribution to the total body clearance of doxacurium can be considered as negligible.

The elimination half-life of doxacurium was reported to be 70 to 100 minutes, and the total body clearance 1.3 to 2.7 ml/kg/min in adult subjects following doses varying from 15 to 80 μg/kg (Table 3). Liver disease appears to have no significant impact on the pharmacokinetics of doxacurium. In contrast, patients with renal dysfunction tend to clear doxacurium at a slower rate than normal patients do (Table 3, Cook et al, 1991). The impact of age on the pharmacokinetics of doxacurium varies from study to study. Gariepy et al (1993) reported significantly decreased plasma clearance and increased elimination half-life in the elderly, and these changes were attributed to a reduced urinary excretion observed in the elderly. However, in Dresner's study (1990), no change in clearance and elimination half-life of doxacurium was found in the elderly, and this was attributed to the comparable urinary excretion between young and elderly patients. The discrepancies between those two studies may be caused by the selection criteria of age for elderly patients. Reduced urinary excretion can be observed only in those patients whose age should be old enough (> 75 yr).

Table 3. Pharmacokinetic parameters of doxacurium

Reference	Patient group	No. of patient	Age (mean) (years)	Doxacurium (mg/kg)	Anesthesia	$t_{1/2\beta}$ (min)	Vd_{ss} (L/kg)	CL (L/h/kg)	12h urinary excretion (%dose)
Cook et al.	Healthy adults	9	(32.1)	0.015	Isoflurane/N_2O	99	0.22	0.16	25
(1991)	Renal failure	8	(38.7)	0.015		221	0.27	0.07*	
	Hepatic failure	7	(43)	0.015		115	0.29	0.14	30
DeAngelis et al	Healthy adults	3	21-40	0.08	Fentanyl/N_2O	70	0.12	0.09	
(1990)									
Dresner et al	Healthy adults	8	22-49	0.025	Isoflurane/N_2O	86	0.15	0.13	31
(1990)	Elderly	8	67-72	0.025		96	0.22*	0.15	25
Gariepy et al	Healthy adults	9	19-39	0.030	Isoflurane/N_2O	76	0.23	0.15	25
(1993)	Elderly	9	70-83	0.030		120*	0.25	0.10*	16
Zhu et al	Healthy adults	8	46		Propofol/N_2O				
(1996)									

Abbreviations: $t_{1/2\beta}$ = elimination half-life; Vd_{ss} = volume of distribution at steady-state; CL = total body clearance; * = $p<0.05$ vs healthy adults.

3.3 PHARMACODYNAMICS

3.3.1 Potency

Doxacurium is the most potent neuromuscular blocking drug currently available, with an estimated ED95 of 25 to 30 µg/kg in adults (Basta et al, 1988; Katz et al, 1989; Murray et al, 1988).

3.3.2 Onset and duration of action

Doxacurium has a slow onset and long duration of action. Onset times are very variable and show a lot of individual variability (Table 4). Doses equal to 1xED95 have been reported to produce maximum blockade in times ranging from 3 to 13 minutes, with clinical relaxation during 30 minutes to over 1.5 hour. Increasing the dose will proportionally shorten onset time and prolong duration of action. Renal failure is associated with prolonged duration of action of doxacurium because of the decreased clearance (Cashman et al, 1990; Cook et al, 1991). However, end-stage liver disease makes the duration of action of doxacurium more variable (Cook et al, 1991). Volatile anaesthetics reduce the onset time and increase the duration of blockade because of their potentiating effect on neuromuscular blockade (Swen et al, 1989). In the elderly, the onset time was significantly slower (Dresner et al, 1991; Gariepy et al, 1993; Martlew & Harper, 1995).

3.4 PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIP

Till now, there is only one study that reported doxacurium pharmacokinetic-pharmacodynamic parameters. The equilibrium time delay between plasma concentration and effect, t1/2Keo, was 14 minutes for doxacurium (Gariepy et al, 1993). This value was similar to that of vecuronium and atracurium. The similarity in t1/2Keo among these drugs is consistent with Hennis and Stanski's theory (1985), which states that the main factors contributing to t1/2Keo were blood perfusion and partitioning of the relaxant between blood and muscle. Meanwhile, compared with other neuromuscular blocking drugs, the smaller EC50 (drug concentrations at effect site at 50% of maximum effect) of doxacurium demonstrates its high potency.

3.5 CLINICAL USE

The singular property of doxacurium chloride is the lack of any significant cardiovascular effect. In fact, it appears that this is the only advantage of this drug in clinical use. The main use of doxacurium is when prolonged neuromuscular blockade is required, especially in high-risk patients. Compared with vecuronium and atracurium, its long duration of action makes it less flexible and more likely to produce residual paralysis in the postoperative period.

Table 4. Pharmacodynamic properties of doxacurium

Reference	Patient group	No. of patient	Doxacurium (mg/kg)	Anesthesia	Monitoring	Maximum bolck (%)	Onset[a] (min)	Recovery[b] (min) 25%
Basta et al	Healthy adults	6	0.03	Fentanyl/N_2O	ST, MMG	89.1	10.2	84.3
(1988)		9	0.05			99.6	5.9	82.9
		7	0.08			100	3.5	159.0
Cashman et al	Healthy adults	18	0.025	Halothane/N_2O	TOF, MMG	88.4	10.8	66.7
(1990)	Renal failure	17	0.025			82.6	10.9	120.8
Cook et al	Healthy adults	9	0.015	Isoflurane/N_2O	TOF, EMG	86.1	7.8	36.1
(1991)	Renal failure	9	0.015			98.3	10.8	79.6
	Hepatic failure	9	0.015			70.4	10.6	51.6
Dresner et al	Healthy adults	8	0.025	Isoflurane/N_2O	ST, MMG	96.6	7.7	67.5
(1990)	Elderly	8	0.025			96.4	11.2*	97.1
Gariepy et al	Healthy adults	8	0.03	Isoflurane/N_2O	TOF, EMG	95	8.9	48.1
(1993)	Elderly	9	0.03			96	12.9*	113.4
Goudsouzian et al	Children	8	0.03	Halothane/N_2O	TOF, MMG	90.1	6.6	25.2
(1989)		9	0.05			99.8	3.2	43.5
Katz et al	Healthy adults	9	0.024	Fentanyl/N_2O	TOF, MMG	97	6	55
(1988)								
Kern et al	Children	9	0.052	Alfentanil/N_2O	TOF, EMG	95	18.2	33.7
(1996)		12	0.032	Isodlurane/N_2O		95	8.5*	33.3
		9	0.041	Halothane/N_2O		95	12.7	35.7

Lennon et al	Healthy adults	18	0.05	Fentanyl/	TOF, MMG	95.7	5.4	84.7
(1989)		18	0.08	Enflurane/N_2O		97.7	3.5*	164.7
Martlew	Healthy adults	21	0.03	Fentanyl/	TOF, EMG	100	5.7	79.0
(1995)	Elderly	17	0.03	Isodlurane/N_2O		96	7.7*	66.2
McDonagh et al	Adults with	10	0.05		TOF, MMG	100	6.5	2.75
(1996)	Cardiac disease	10	0.075			100	6.2	4.3*
Murray et al	Healthy adults	7	0.023	Narcotic/N_2O	TOF, MMG	92.4	10.3	57.1
(1988)		9	0.05			100	4.5	124.8
Murray et al	Healthy adults	9	0.0125	Isodlurane/N_2O	TOF, MMG	80	12	32
(1990)		9	0.018			94	9	39
		9	0.023			99	9	59
Samer et al	Children	9	0.0275	Halothane/N_2O	TOF, EMG	91	6.7	27.8
(1988)		8	0.05			99	5.3	50.6
Scott & Norman	Healthy adults	9	0.0375	Fentanyl/N_2O	TOF, EMG	83.6	10.5	51
(1989)		18	0.0625			97.6	9.85	101.7

a: Time to maximum blockade or time to 90%, 95% blockade where individual studies are indicated.

b: Time for T1(first train-of-four response or single twitch) to recover spontaneously to 25% baseline (clinical duration of effect).

Abbreviations: * = $p<0.05$ vs comparator patient group; N_2O= nitrous oxide; ST= single twitch stimulation; TOF= train-of-four stimulation; MMG= mechanomyography; EMG= electromyography.

Intubating doses (2xED95) should not be administered for surgery of less than 2 hours anticipated duration.

4. PHARMACOKINETIC/PHARMACODYNAMIC MODELING

Efficacy and safety of drug treatment are largely dependent on the dosing regimen. Not surprisingly, dose finding is an important aspect of drug development. Pharmacokinetic considerations play an important role in developing dosing regimens of new drugs. Important progress has been made, however, with a more comprehensive approach based on modeling of the relationship between pharmacokinetics and pharmacodynamics. Such modeling allows the characterization and prediction of time course of drug action rather that concentration and provides a scientific basis for development of the dosing regimen.

An integrate PK-PD model includes three parts: PK model; PD model; and link model (Fig 9). A PK model deals with what the body acts to the drug, and relates dose to plasma drug concentration (Cp). In PK modeling, the focus of interest is the process controlling drug concentration at any time after dose, such as absorption, distribution, metabolism, and excretion procedure. In contrast, the PD model describs what the drug acts to the body, and relates drug concentration at effect site (Ce) to drug effect (E). In PD modeling, the focus of interest is the relation between the Ce and the effect. The relationship between Cp and Ce can

be determined by a link model, which combines PK model with PD model, and converts Cp to Ce. Three models, linked in series, can be used to analyze combined pharmacokinetic and pharmacodynamic data arising from non-steady-state experiments, describe the overall concentration-effect relationship, and lead to useful insights into rational dose regimen design.

Figure 9 graphically shows the steps of PK-PD modeling and the relationship among plasma concentration (Cp), drug concentration at effect site (Ce) and pharmacological effect (E). After drug administration, the drug effect often lags behind the time profile of the drug concentration in plasma. This becomes obvious from a plot of the effect to the drug plasma concentration showing counterclockwise hysteresis loop: connecting points in time order show two distinct limbs, ascending (Cp rising) and descending (Cp falling) (Fig. 9). The time delay between changes in drug plasma concentration and effect reflects in general the time that the drug requires to distribute to the effect site and to elicit its response, or the equlibration delay between plasma concentration and effect. To suppress hysteresis and reveal the true underlying concentration-effect curve during non-steady state experiments, the effect was modeled as a new kinetic "compartment", linked to one of the PK compartments by a first order process but receiving only a negligible amount of drug. As a consequence, the effect compartment does not affect the pharmacokinetics of the drug. The effect compartment concentration is a hypothetical concentration and can never be measured. The hypothetic effect compartment was first proposed by Segre

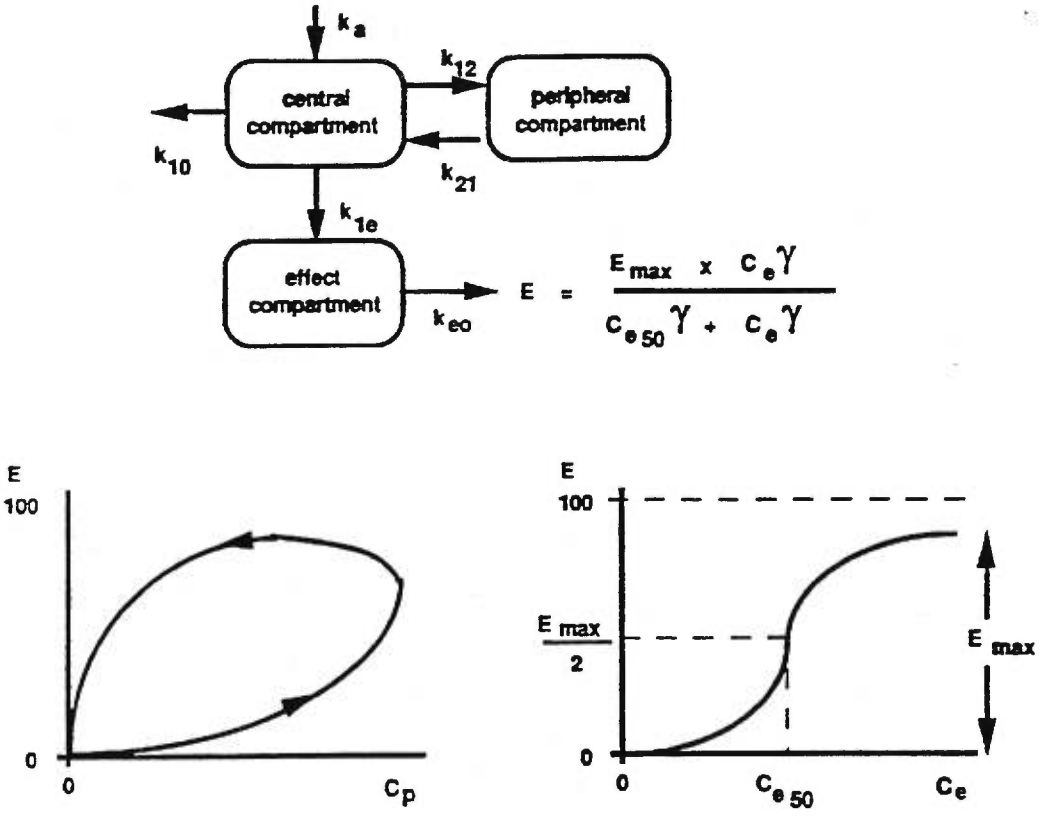
(1968) and subsequently elaborated by Sheiner (1979) and Holford & Sheiner (1981; 1982). Kinetically, the first-order rate constant Keo and the equilibration half-life t1/2Keo describe the delay and thus are relevant parameters for the rate of onset of the drug effect. This equilibration rate constant can be derived by minimizing the differences between the ascending and descending limbs of the hysteresis curve. When Keo is optimal, hysteresis curve is collapsed to a single curve (Fig. 9), and a full description of the effect compartment concentration vs, effect relationship, which represents the steady-state plasma concentration vs effect relation, can be estimated using the appropriate PD model, often the sigmoid Emax model. Two parameters describing the PD model: EC50 (effect compartment concentration of drug at 50% effect) and γ (the slope factor of sigmoid curve) can also be derived. Based on these parameters, the pharmacological effect of drug can be predicted as a function of time.

The additional advantage of PK-PD modeling with a separate effect compartment is the information on equilibration or onset of action, duration of effects, the individual's sensitivity and the maximal response when achievable.

Based on the characteristics of PK, PD, and link model, there are three different approaches for PK/PD modeling: parametric, non-parametric and Rtot PK/PD modeling.

FIGURE 9

Pharmacokinetic-pharmacodynamic modelization



Effect compartment linked to a two-compartment pharmacokinetic model (upper part). Effect (E) against the drug concentration in plasma (Cp) and in the effect compartment (Ce) (lower part) (adapted from Van Peer A. et al, 1993)

4.1 PARAMETRIC PK/PD MODELING

This approach of PK/PD modeling was first successfully applied to d-tubocurarine (Sheiner et al, 1979). In this instance, a model was used that is presently often referred to as a full parametric model. This type of modeling requires prior knowledge of the pharmacokinetic model to describe the concentration-effect relationship, and the link model that characterizes the equilibration kinetics between blood and the hypothetical effect compartment.

The procedure for the parametric PK-PD modeling is as follows: PK parameters are estimated first by fitting an appropriate PK model to the plasma drug concentration (Cp) vs time data. If the PK model is, in fact correctly specified, then, fixing the PK parameters to these estimates. The second stage is link model to derive Ce. Then an appropriate PD model is fit to the effect vs time data, assuming the link model. The form of the underlying PK, PD, and link models are all assumed to be known a priori.

Parametric models are in common use for several reasons: the data are described with brevity by quoting the parameter estimates, the influence of different factors on the data can easily be compared in terms of parameter estimates; and the estimates can be used for interpolation/extrapolation or simulation. In the absence of model misspecification, the parametric method usually gives a better estimation of the PD model than the non parametric

method, as the parametric method has valid assumptions about the true PK model, the true PD model, and the true link model, while the non parametric method "knows" only the link model. However, in the presence of PK model misspecification, non parametric method can be of considerable benefit.

4.2 NON-PARAMETRIC PK/PD MODELING

In according to the full parametric method, non-parametric approaches to link model have been proposed. These approaches differ mainly with respect to the prior knowledge required. The non parametric approach involves a non parametric link submodel, but retains parametric PK model (Fuseau et al, 1984). The value of Keo is estimated as the value that causes the hysteresis curve (concentration vs effect intensity connected in time order) to collapse to a single curve that represents the steady-state concentration-effect relationship. Thus the value of Keo is estimated without postulation of particular parametric model for the concentration-effect relationship. The method has the important advantage that it allows inspection of the concentration-effect relationship, before selecting a particular pharmacodynamic model. In this way the risk of model misspecification is minimized.

On the basis of Fuseau's model, Unadkat et al (1986) took one step further: the PK model is also approximated non-parametrically. This approach may be of value in exploratory data analysis and in situations where the pharmacokinetics

can not be easily characterized on basis of a compartmental PK model (e.g., sustained release preparations).

When the underlying PK and, presumably PD models can validated a priori, the parametric method is preferred because it produces precise estimation of the PD model. In reality, however, the true model is never known, and one can rarely be certain that model misspecification is absent. Therefore, the non-parametric approach may offer a distinct advantage for routine analysis of PK/PD data.

4.3 Rtot PK/PD MODELING

This approach is on the basis of no- parametric PK/PD modeling with a modified effect compartment, which included a total concentration of receptors (Rtot) (Donati & Meistelman, 1991). It is assumed that the effect compartment contains a finite concentration of receptors. The neuromuscular blocking drug is either free or bound in a 1 : 1 molar ratio to the receptor. The transfer of drug from central compartment to effect compartment is assumed to be proportional to the concentration gradient of the free drug. Total concentration of drug in the effect compartment is equal to free plus bound drug concentration. Neuromuscular blockade occurs only when a large proportion of receptors are occupied (Paton & Waud, 1967).

In this approach, Keo and Rtot were estimated according to non-parametric PK/PD modeling (Unadkat et al, 1986). The optimal Keo and Rtot were those that minimized differences between calculated and measured effect. Based on the optimal Keo and Rtot, effect compartment concentrations, which correspond to free drug levels, were then derived.

The validity of this approach has been proved with vecuronium, and it shows that inclusion of a finite concentration of receptors in the effect compartment improves the goodness of fit between predicted and experimental data (Ducharme et al, 1994).

5. THE OBJECTIVE OF THE STUDY

For most drugs, there is a lag time between plasma concentration and effect which is described by an equilibration rate constant (Keo). In many pharmacokinetic-pharmacodynamic studies on neuromuscular blocking agents, a short infusion is selected instead of a bolus administration even though neuromuscular blocking agents are usually given as bolus in clinical practice (Rupp et al, 1987; Sohn et al, 1986; Shanks et al, 1987; Weatherley et al, 1983). This type of administration is preferred because compartmental analysis assumes instantaneous and homogeneous mixing of drug in all compartments at all times, which is not the case after a bolus dose. A short infusion also allows collection of an adequate number of blood samples during onset of action.

However, recent studies have shown that it is possible to derive valid pharmacokinetic-pharmacodynamic relationships after bolus administration when arterial blood can be drawn using a rapid sampling schedule in the first 2 minutes (Ducharme et al, 1993; 1995), and the equilibration half-life (t1/2Keo) is then derived using a non-compartmental PK-PD model. But, using this approach, the t1/2Keo derived after an intravenous bolus of two neuromuscular blocking drugs: vecuronium and atracurium, were consistently longer than those reported by other investigators after short infusion administration (Rupp et al, 1987; Sohn et al, 1986; Shanks et al, 1987; Weatherley et al, 1983). Since in clinical practice,

intermediate and long acting muscle relaxants are usually administered as an intravenous bolus dose, this discrepancy warranted clarification.

Paton and Waud reported the existence of a safety margin for neuromuscular transmission. The time required to reach this threshold may differ according to the type of administration. For vecuronium, when receptor occupancy was taken into account to the data after a bolus dose, the resulting Keo was faster and reached a value similar to that after an infusion. Therefore, receptor occupancy was thought to play a major role in the difference in Keo between bolus and infusion of vecuronium. However, this proved not to be the case for atracurium. The input rate into the central compartment was then questioned.

The objective of the present study was to evaluate the impact of the input rate, i.e., iv bolus vs short infusion, on Keo estimation. For this investigation, doxacurium was chosen because of its high potency. For a drug with high potency, the role of receptor occupancy is expected to be more important.

ARTICLE

PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF DOXACURIUM: EFFECT OF INPUT RATE

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ABSTRACT

One of the basic assumptions in pharmacokinetic-pharmacodynamic modeling (PK-PD) is that drug equilibration rate constant between plasma concentration and effect (Keo) is not changed by input rate. In order to test this assumption in a clinical setting, a 25µg/kg IV dose of doxacurium was administered either by bolus injection or 10 min-infusion to fifteen anaesthetized patients. Neuromuscular function was monitored using train-of-four stimulation of the ulnar nerve. For the short infusion dose, arterial concentrations were measured at 1-min intervals during infusion and at frequent intervals thereafter. Following the IV bolus dose, the early PK profile of doxacurium was investigated by measuring doxacurium arterial concentrations every 10 seconds during the first 2 minutes and at frequent intervals thereafter. PK-PD modeling was performed using non-parametric approach with and without including a finite receptor concentration (R_{tot}) in the effect compartment. Kinetic parameters were unchanged. For the bolus and the infusion, Keo values were 0.053 ± 0.006 min^{-1} and 0.056 ± 0.009 min, respectively. Using the Rtot model, corresponding Keo values were 0.148 ±

0.016 and 0.150 ± 0.024, respectively. The relatively faster Keo obtained with the Rtot model is compatible with the high potency of doxacurium. In conclusion, our results show that PK-PD parameters derived with either a bolus or an infusion mode of administration, are equally reliable.

KEY WORDS: pharmacokinetics, pharmacodynamics, neuromuscular blocking agents, doxacurium, input rate, intravenous, bolus, infusion

INTRODUCTION

For most drugs, there is a lag time between plasma concentration and effect which is described by an equilibration rate constant (K_{eo}). Being a constant, the input rate, i.e bolus or short-infusion, should have no effect on Keo estimation, if the study is properly designed. Even though neuromuscular blocking agents are usually given as a bolus in clinical practice, a short infusion is selected instead of a bolus administration for pharmacokinetic-pharmacodynamic (PK-PD) studies (1-4). This mode of administration is preferred because compartmental analysis assumes instantaneous and homogeneous mixing of drug in all compartments at all times, which is not the case after a bolus dose. After a short infusion, it is also easier to collect an adequate number of blood samples during onset of action.

Recent studies have shown that it is possible to derive pharmacokinetic-pharmacodynamic parameters after bolus administration of vecuronium and atracurium when arterial blood is drawn using a rapid sampling schedule in the first 2 min (5, 6). The equilibration half-life ($t_{1/2}$ keo) is then derived using a nonparametric PK-PD model. Using this approach, the $t_{1/2}$keo derived after an iv bolus dose of these two muscle relaxants were consistently longer than those reported elsewhere after a short infusion administration (1-4). Since intermediate and long acting muscle relaxants are usually administered as an iv bolus dose in clinical practice, this discrepancy warranted clarification.

The effect compartment, by virtue of its high receptor density, is considered a significant drain for drug molecules and clinically detectable neuromuscular block does not occur until a large proportion of receptors has been occupied, 5% to 95% block corresponding to 75%-92% receptor occupancy (7). Therefore, the

time required to reach this treshold may differ according to the mode of administration. When a model taking into account receptor occupancy (8), the Rtot model, was applied to the same data sets obtained after bolus administration of vecuronium, the resulting K_{eo} were faster than those observed with the traditional model and were similar to those reported after an infusion (9). The difference in K_{eo} between bolus and infusion administrations was therefore mainly attributed to the time needed to overcome the safety margin of neuromuscular transmission. When this model was subsequently applied to data obtained after an iv bolus of atracurium (6), a less potent muscle relaxant, the equilibration rate was not increased (unpublished data). Therefore, receptor occupancy appeared to be a limiting factor for vecuronium, a potent drug, but could not explain the slower Keo obtained for atracurium after an IV bolus. The input rate into the central compartment was then questioned.

The objective of the present study was to determine if the input rate, i.e iv bolus vs short infusion, has any impact on Keo estimation, in a clinical setting. For this investigation, a drug with a high potency was chosen because the role of receptor occupancy is expected to be more important. A secondary objective was to compare PK-PD parameters obtained with and without the Rtot model.

METHODS

Clinical Protocol

Patients. The protocol was approved by the Hospital Ethics Committee and all patients gave written informed consent prior to entering this study. Fifteen ASA physical status I or II adults (age range, 20 to 62 years), scheduled for elective surgery where the insertion of an arterial cannula was indicated, participated in this study. Patients were randomized into two groups : iv bolus and 10 min infusion. Patients in each group were matched by age and gender (Table I). Patients with cardiovascular, neuromuscular, pulmonary, hepatic or renal disease were excluded. Individuals deviating from ideal body weight by more than 25% or patients taking medications known or suspected to affect neuromuscular function, did not qualify for entry.

Anesthesia. If needed, patients were premedicated with either lorazepam 2mg sc, midazolam 5mg im, meperidine 50mg im, hydroxyzine hydrochloride 50mg im, or oxazepam 15mg po. During surgery, electrocardiography, blood pressure and pulse oxymetry were monitored continuously. Inspired and expired carbon dioxide, oxygen and nitrous oxide were measured. Core temperature was kept above 35°C. Anaesthesia was induced with alfentanil (20 to 30 μg/kg) and propofol (1.5 to 3 mg/kg), maintained with nitrous oxide (70%) in oxygen and by continuous infusion of propofol (10 to 15 mg/kg/hr). Intubation of the trachea was performed without the use of muscle relaxants. Premedication and anesthetic procedure were similar in both groups.

Neuromuscular monitoring. A vein in the antecubital fossa was cannulated for drug injection and fluid replacement. In the same arm a supramaximal train-of-four (2 HZ for 2 sec every 20 sec) electrical stimulation was applied to the ulnar nerve at the wrist via surface electrodes. The resultant force of contraction of the adductor pollicis was measured using a force transducer (Grass FT-10, Grass Instrument Co., Quincy, Massachusetts, USA). In the opposite arm, blood samples were collected via a 20 gauge cannula inserted in the radial artery. The cannula was connected to a 3-way stopcock via a small extension tube. Blood flow was approximately 3ml every 10 sec at normal arterial blood pressure. Neuromuscular function was monitored after loss of consciousness and throughout anaesthesia, for at least 120 min. Vecuronium was administered when additional muscle relaxation was required. At that time, however, neuromuscular monitoring would be discontinued. At the end of surgery, neostigmine (0.06 mg/kg) and atropine (0.02 mg/kg) were administered to reverse any residual curarisation.

Sampling. Arterial blood samples were collected into heparinised tubes, the first sample was taken before doxacurium administration. After stabilization of anaesthesia and of the train-of-four (TOF) response, the bolus group (n=8) received 25µg/kg of doxacurium chloride by iv bolus over 2 sec, and the infusion group (n=7) received the same dose at a constant rate over a 10 min period. For the bolus group, the 3-way stopcock was opened at the end of the doxacurium bolus injection and blood was allowed to flow out of the arterial cannula for 2 min, changing tubes every 10 sec. The time assigned to each sample was the midpoint of the interval over which the sample was drawn. Further samples (3ml) were then collected at 3, 5, 7, 10, 20, 30, 45, 60, 90, 120, 180, 240 and 300 min (when possible). For the infusion group, blood samples were collected every

minute during the 10 min infusion period, then at 1, 2, 3, 5, 7, 10, 20, 30, 45, 60, 90, 120, 180, 240 and 300 min (when possible) after the infusion. Three additional samples corresponding to 25%, 50% and 75% neuromuscular recovery were also taken in both group. Blood samples were centrifuged and the plasma was stored at -70°C until analysis.

HPLC analysis. Doxacurium plasma concentration was determined using an HPLC assay developed in our laboratory (10). This method proved to be sensitive (limit of quantification, 4ng/ml), precise (mean coefficient of variation, 6.9%) and accurate (mean, 98.3%; coefficient of variation, 4.8%). It is linear for doxacurium concentrations ranging from 4 to 2000 ng/ml (r^2 of 0.9993). Samples with concentrations higher than the upper limit of the validated range were diluted with blank plasma.

Pharmacodynamic analysis. Neuromuscular block was defined as the depression of the twitch response to the first stimulation in the train-of-four (T1) and expressed as a percentage of the baseline value obtained prior to the administration of doxacurium. Neuromuscular block was measured at each sampling time, except for blood samples drawn every 10 sec e.g. during the first 2 min after the bolus administration.

Noncompartmental pharmacokinetic-pharmacodynamic modelling

Noncompartmental PK analysis. Noncompartmental pharmacokinetic analysis allowed the calculation of the area under the plasma concentration-time curve (AUC) and the area under the first moment curve (AUMC) according to the trapezoidal rule (11). The mean residence time (MRT) was derived from the

AUMC:AUC ratio. The total clearance (CL) was obtained by dividing dose by AUC, and the volume of distribution at steady-state (V_{dss}) by the product of MRT and CL. The elimination half-life ($T_{1/2}$) was obtained from linear regression of the terminal portion of the plasma concentration vs time curve. The maximum plasma concentration (C_{max}) and the time from injection to C_{max} (T_{max}) were noted.

Non parametric link model. The rate of transfer of doxacurium into the effect compartment (K_{eo}) was estimated according to the method of Unadkat et al (12) using a Basic program (13) with the input of time, its corresponding doxacurium plasma concentration and percentage of neuromuscular block. Accordingly, the loop was collapsed by finding the value of Keo that minimizes the average of the squared vertical distances between the ascending and descending limbs of the hysteresis curve (percentage block *vs* plasma concentrations). Doxacurium effect compartment concentrations were derived for each time point according to this optimal value.

R_{tot} link model. The same values of concentration and neuromuscular block were fitted to the non parametric link model which was modified to include a finite concentration of pharmacological receptors (Rtot or R in the original paper) in the effect compartment (8). In the classical model, it is tacitly assumed that the fraction of drug bound to the receptor (RD) is negligible compared to the total drug in that compartment (e.g D_f and RD). This may not be the case in presence of a high density of receptors (as it occurs at the neuromuscular junction) or when the drug has a high affinity for these receptors (e.g. doxacurium). Then, the concentration of bound drug in the effect compartment (RD) may become nonnegligible with respect to the concentration of free drug (D_f). In this case, the

Rtot model would be more appropriate than the classical model. As for the other assumptions in the R_{tot} model, they are similar to those in the classical model: a) the neuromuscular blocking drug is either free or bound to the receptor in a 1:1 molar ratio; b) drug transfer between the central compartment (plasma) and the effect compartment (neuromuscular junction) is determined by the concentration gradient of the free drug. Using the R_{tot} program, the optimal K_{eo} and R_{tot} which minimize the average of the squared vertical distances between the ascending and descending limbs of the hysteresis curve (percentage block *vs* plasma concentrations) were estimated. These values were then used to derive the effect compartment concentrations. The R_{tot} model has already been validated using vecuronium as drug model (9).

Sigmoid Emax pharmacodynamic model. For both link models, doxacurium effect compartment concentrations were correlated with neuromuscular block (weight=1) using the sigmoid E_{max} model (Sigma-Plot Software, Jandel Scientific, CA, USA) (14). Two parameters were derived by successive iterations to give the best fit: EC_{50}, the effect compartment concentration at 50% block, and γ, the slope factor of the sigmoid curve.

Statistical Analysis.

Results are presented as mean ± standard error of the mean (SEM). The comparisons of kinetic and dynamic parameters between iv bolus and short infusion group were done using unpaired Student's t-test. Intra-group comparisons were done using Student's t-test for paired data. The level of statistical significance was fixed at 0.05.

For both Unadkat and R_{tot} models, goodness of fit was estimated as follows. At any given time, residuals ie the difference between the estimated and the true effect was expressed as a percentage of the true effect. The mean of the squared residuals (MSQU) obtained for each model were then compared using Student's t test for paired data.

RESULTS

Pharmacokinetics. Demographic data of the study population are shown in Table I. Individual doxacurium plasma concentration-time profiles after iv bolus or infusion are represented in Figure 1. Following the iv bolus dose of doxacurium, C_{max}s of doxacurium were reached in the third (20-30 sec, n=2), fourth (30-40 sec, n=2), fifth (40-50 sec, n=2) and sixth (50-60 sec, n=2) arterial sample, for an average C_{max} and T_{max} of 2395 ± 348 ng/ml and 0.7 ± 0.1 min, respectively (Fig 1). After the 10-min infusion, mean C_{max} was 440 ± 67 ng/ml .

No significant difference in $AUC_{0\text{-}inf}$ could be found between bolus and short infusion administration (21904 ± 3076 ng/ml·min vs 25294 ± 6575 ng/ml·min). Consequently, noncompartmental pharmacokinetic parameters, including CL, MRT, Vdss and $T_{1/2}$, did not differ significantly between the two groups (Table II).

Pharmacodynamics. The onset time to maximum neuromuscular block was significantly prolonged in patients with short infusion compared with iv bolus (17.9 vs 11.0 minutes). One patient in the bolus group and two patients in the short infusion group could not reach maximum block over 75% after a 25μg/kg doxacurium, and two patients in the infusion group could not attain 50% recovery because vecuronium was required for additional muscle relaxation. Thus, the number of subjets included in the analysis of recovery times varied. Recovery to 25, 50 or 75% did not significantly differ between the two groups and recovery index from 25 to 75% remained unchanged (47.3 vs 43.4 minutes). Maximum block for both groups were similar (Table III).

Pharmacokinetic-pharmacodynamic modelling. Figure 2 compares in 2 representative patients the different steps of PK-PD modelling with Unadkat et al nonparametric model and R_{tot} model for the short infusion (left panel) and iv bolus data (right panel). Firstly, plotting doxacurium plasma concentration .vs neuromuscular block demonstrated the anticlockwise hysteresis (a,e), which was collapsed to obtain the K_{eo} from which effect compartment concentrations could then be derived (b,f). The neuromuscular block were then plotted against the effect compartment concentrations and a sigmoid was fitted through the data points (c,g). The parameters describing the fitted sigmoid curve were used to predict the neuromuscular block, which was compared with the experimental block (d,h).

For both groups, the R_{tot} model led to a shift to the left of the sigmoid curve, compared with Unadkat et al model (fig 2, c and g). As a result, the EC_{50} and values calculated from the R_{tot} model were significantly decreased (Table IV). The mean molar concentration of receptor that best fitted the experimental data of iv bolus and short infusion were 0.28 and 0.29 μmol/L, respectively. Moreover, including this term in the PK-PD analysis gave rise to a significantly faster K_{eo} than that obtained without it (0.148 vs 0.053min^{-1} for iv bolus and 0.150 vs 0.056min^{-1} for short infusion).

There was no difference in the mean estimated K_{eo} values between iv bolus and short infusion group using either Unadkat et al model (0.053 vs 0.056 min^{-1}) or R_{tot} model (0.148 vs 0.150 min^{-1}). Similarly, the EC_{50} and γ values were comparable between the two groups (Table IV). Although the R_{tot} model gave rise to the significant changes in K_{eo}, EC_{50} and γ values, the variations of these parameters were proportional in both groups.

Based on the K_{eo}, EC_{50} and γ values, neuromuscular block was predicted as a function of time. As illustrated in Figure 3 with mean values ± SEM, the residuals were less using R_{tot} model whether bolus injection or short infusion were given. It was especially the case during the onset phase. For both infusion and bolus groups, goodness of fit was better with the R_{tot} model as indicated by the significantly lower MSQU (Table IV). In addition, there was no significant difference between the onset times predicted with the Rtot model for the bolus and infusion regimen (13.4 ± 2.0 and 19.2 ± 0.83 min, respectively) and that actually observed in patients (Table III). However, this was not the case for the nonparametric model where the corresponding values were 20.6 ± 3.0 and 25.7 ± 3.0 min, respectively. These results suggest that the predictive value for the onset time is better with the R_{tot} model.

DISCUSSION

The accuracy of pharmacokinetic and pharmacodynamic parameter estimation has been shown to depend on methodological factors such as sampling schedule, sampling site as well as the anaesthetic procedure (5, 13, 15). Following a bolus dose of muscle relaxant, plasma concentrations abruptly rise during the first 35 -45 sec until peak is observed (5,6). Using a traditional sampling regimen, this "early" plasma concentration - time profile cannot be adequately characterized which often results in an underestimation of the AUC derived non parametrically (5). This effect is even more pronounced for mivacurium which has a very short half-life (16). Donati et al (13) have previously advocated arterial drug concentrations as providing more accurate representation of the amount of drug actually delivered to the neuromuscular junction. Arterial sampling is especially important immediately following the intravenous injection when arteriovenous differences are most significant (13, 17, 18). The use of venous concentrations can potentially underestimate the drug concentration reaching the neuromuscular junction, which in turn results in overestimated PK variables (13,17) and PK-PD parameters (13). Our protocol was designed in light of the knowledge that choice of background anaesthetic warranted careful consideration. Succinylcholine was not used for intubation since it has been shown to interact with atracurium and affect its pharmacokinetics and PK-PD relationship (19). The potentiating effect of isoflurane on neuromuscular block of muscle relaxant (15, 20) was also avoided by using propofol for maintenance of anaesthesia as propofol is not believed to have potentiating effect at therapeutic concentrations in humans (21).

Doxacurium was selected for its relatively slow onset time thus enabling us to obtain a sufficient number of data points during onset of block. Therapeutic doses of doxacurium can achieve maximum block within 10-15min (10, 22). Another advantage of doxacurium was the absence of any active metabolite thus simplifying PK-PD data interpretation. As all factors known to influence kinetics and/or dynamics (including those listed above) were avoided, doxacurium parameters reported herein are therefore thought to be representative estimates of its pharmacokinetics and pharmacodynamics following iv bolus or short infusion administration.

As might be expected, doxacurium pharmacokinetic parameters reported herein did not differ between both modes of iv administration. However, the Vd_{SS} and CL appeared to be considerably lower than those reported in other PK studies (10, 23, 24). Earlier doxacurium PK studies have been based either on traditional sampling regimen after an iv bolus injection (10, 23, 24) or have used venous blood samples (10, 23). In view of doxacurium's long half-life, these methodological factors cannot account for such a difference and, in our opinion, the distinct haemodynamic effects of isoflurane and propofol are most probably responsible for this difference.

Immediately after bolus injection, elevated initial concentrations led to increased drug delivery to neuromuscular junction per unit time. Thus, less time was required to overcome the safety margin of neuromuscular transmission (7). Since the duration of action of many muscle relaxants is largely determined by the rate of drug elimination (31) which is not influenced by the mode of iv administration, similar duration of action and rate of recovery were observed in both groups.

The purpose of this study was to assess if K_{eo} varies depending on the mode of iv administration, ie bolus and short infusion. Following a short infusion of muscle relaxant, drug molecules gradually occupy the critical number of receptors at the neuromuscular junction, which allows greater inclusion of data points during the ascending phase of both plasma concentration and neuromuscular block. The other advantage of infusion technique is occurrence of a better "mixing" within the central compartment at all times. After a bolus injection, traditional sampling regimens are unable to accurately assess the "early" time-course of plasma concentrations and parametric PK-PD modeling may result in a slight overestimation of K_{eo} (5). After a bolus, less data points of plasma concentration are also obtained during onset of block than during recovery phase. Uneven distribution of data points between onset and recovery could lead to miscalculation of PK-PD parameters (9). This explains why a short infusion technique coupled to a parametric PK-PD modeling was often preferred by investigators for the determination of muscle relaxant PK-PD parameters (1-4). The number of data points collected during onset can nonetheless be improved by intensive arterial blood sampling following a bolus injection (5,6). It may be argued that sampling during the intravascular mixing phase could be hazardous since drug concentrations are not yet homogenous in the central compartment. This dilemna can be circumvented by non parametric PK-PD analysis.

Non parametric PK-PD modeling of doxacurium was performed for both modes of administration using a program previously validated for bolus doses of vecuronium and atracurium (5, 6). In our study, the continuous arterial blood sampling during the first 2 min provided an accurate description of the "early" kinetics of doxacurium. A balanced number of data points for both onset and recovery phases yielded an accurate sigmoid curve where the bias of one phase

over the other was effectively avoided. Mean $t_{1/2}$ Keo values of 13 and 12.4 min were obtained following doxacurium iv bolus and infusion, respectively. Although, a similar equilibration half-life was previously reported for doxacurium by our group (10), the validity of the comparison may be questionnable in view of all the confounding effects resulting from differences in methodology. On the other hand, EC_{50} values were shown to be markedly increased in the present study, which is compatible with the absence of potentiating effect of propofol (21). To our knowledge, no other PK-PD data for doxacurium have been so far published by other investigators.

The R_{tot} model was also used in this study to evaluate doxacurium PK-PD relationship. Inclusion of a finite concentration of receptors in the effect compartment improved the goodness of fit for doxacurium as it has been shown to do with vecuronium (9). The mean receptor concentrations obtained in this study (0.28μmol/L after bolus injection, 0.29μmol/L after short infusion) are consistent with previous estimates of receptor density in the synaptic cleft (8). Moreover, this study demonstrated that application of this R_{tot} model was associated with a significantly faster equilibration delay (approximately 4.5 min) for doxacurium, as it was previously observed with vecuronium (9). Since doxacurium and vecuronium are more potent than atracurium, this finding reinforces our conviction that receptor occupancy could be a limiting factor for potent drugs (8).

Despite of a markedly faster onset time after bolus injection than after short infusion of doxacurium, K_{eo} values did not differ significantly. A similar observation was made when two bolus doses of atracurium were given at 1-hour interval: a faster onset time and an unchanged K_{eo} were observed after the

second dose (6). The present study provide additionnal evidence that onset time and K_{eo} are governed by different factors. Therefore, K_{eo} estimation of muscle relaxant probably takes into account mainly pharmacokinetic factors. Thus, the values obtained after a rapid bolus are comparable to those seen after an infusion.

In conclusion, this clinical study represents the first attempt to compare the impact of input rate to the central compartment, ie bolus injection vs short infusion, on K_{eo} estimation. In addition, this is the first study to characterize doxacurium "early" pharmacokinetics using an extensive blood sampling procedure during the intravascular mixing phase. No difference in doxacurium K_{eo} values was found between both modes of iv administration, which suggests that K_{eo} is not influenced by the rate of input into the central compartment.

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LEGENDS FOR ILLUSTRATIONS:

Figure 1. Temporal profiles of doxacurium plasma concentration and neuromuscular blockade in patients following an iv bolus or a short infusion of doxacurium chloride 25 μg/kg.

Figure 2. Comparison of doxacurium pharmacokinetic-pharmacodynamic modeling following the iv bolus (**a, b, c, d**) or short infusion (**e, f, g, h**) of doxacurium 25 μg/kg in two patients

a, **e**) Effect - plasma concentration anticlockwise hysteresis.

b, **f**) Effect compartment concentration-time profiles.

c, **g**) Effect - effect compartment concentration sigmoidal curves.

d, **h**) Predicted effect-time curves.

Figure 3. Mean percent residuals ± SEM between simulated and experimental data for all patients included in the study. Simulations were obtained using Unadkat et al non parametric PK-PD model (—)and R_{tot} PK-PD model (—).

Table I. Patient Characteristics

	IV bolus	Short infusion
ASA Physical Status		
I/II	4/4	3/4
Gender		
Female/Male	3/5	2/5
Age (yr)	46 ± 5	49 ± 5
Weight (kg)	71 ± 3	71 ± 3

ASA, American Society of Anesthesiologists.

Values are mean ± SEM.

Table II. Noncompartmental pharmacokinetic parameters of doxacurium

	$AUC_{(0\text{-}inf)}$ (ng/ml*min)	CL (ml/kg/min)	MRT (min)	Vd_{ss} (L/kg)	$T_{1/2}$ (min)
IV bolus	21904 ± 3076	1.192 ± 0.133	119.4 ± 11.0	0.138 ± 0.015	106.7 ± 9.0
Short infusion	25294 ± 575	1.141 ± 0.147	128.5 ± 17.5	0.137 ± 0.020	106.1 ± 15.3

Values are mean ± SEM

Table III. Doxacurium pharmacodynamics

	IV bolus	Short infusion
Onset to		
Maximum block (min)	11.0 ± 1.2	17.9 ± 1.1*
Maximum block (%)	82.3 ± 3.0	81.9 ± 5.4
Recovery until		
25% baseline (min)	27.3 ± 6.3[a]	39.0 ± 3.0[b]
50% baseline (min)	48.8 ± 7.5	49.4 ± 6.9[b]
75% baseline (min)	72.5 ± 9.0	75.6 ± 8.8[b]
Recovery index		
from 25 to 75% (min)	43.4 ± 4.6[a]	47.3 ± 7.3[c]

Values are mean ± SEM; *: $P<0.05$; a: n=7, b: n=5, c: n=3

Table IV. PK-PD modeling of doxacurium

	IV bolus	Short infusion
Non parametric model		
K_{eo} (min^{-1})	0.053 ± 0.006	0.056 ± 0.009
EC_{50} (ng/ml)	128.6 ± 17.0	126.7 ± 15.7
γ	5.8 ± 0.5	5.3 ± 0.9
MSQU	136 ± 32	32 ± 10
R_{tot} model		
R_{tot} (µmol/L)	0.28 ± 0.03	0.29 ± 0.07
K_{eo} (min^{-1})	0.148 ± 0.016*	0.150 ± 0.024*
EC_{50} (ng/ml)	121.6 ± 17.5*	117.3 ± 19.7
γ	3.7 ± 0.4*	2.9 ± 0.3*
MSQU	25 ± 10*	5.5 ± 1.6*

Values are mean ± SEM; *: P<0.05 vs nonparametric model.

FIGURE 1

iv bolus
Short infusion
Plasma concentration. (ng/ml)
Neuromuscular blockade (%)
Time (min)
10000
1000
100
10
1
100
80
60
40
20
0
0
10
20
30

FIGURE 2

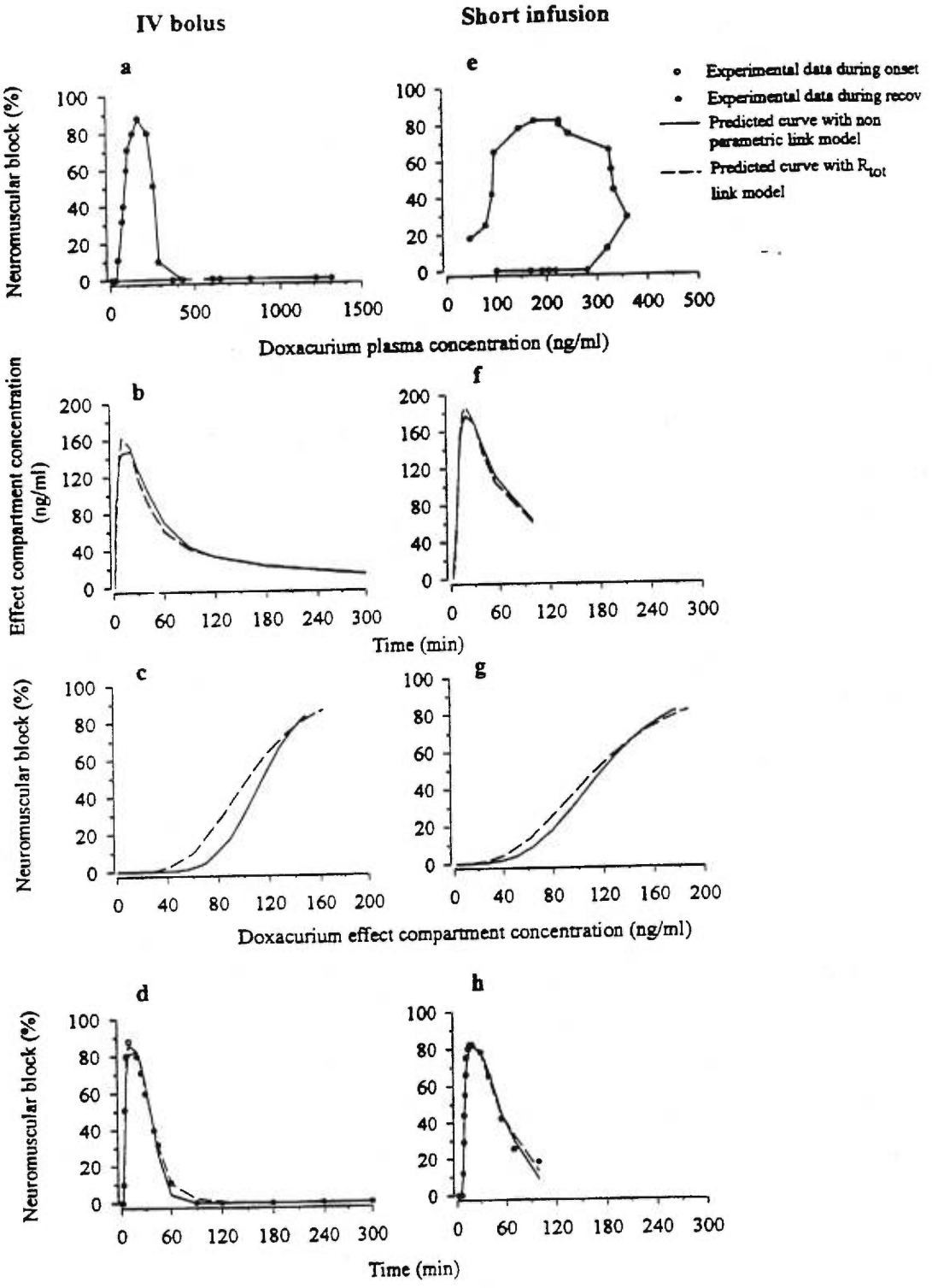
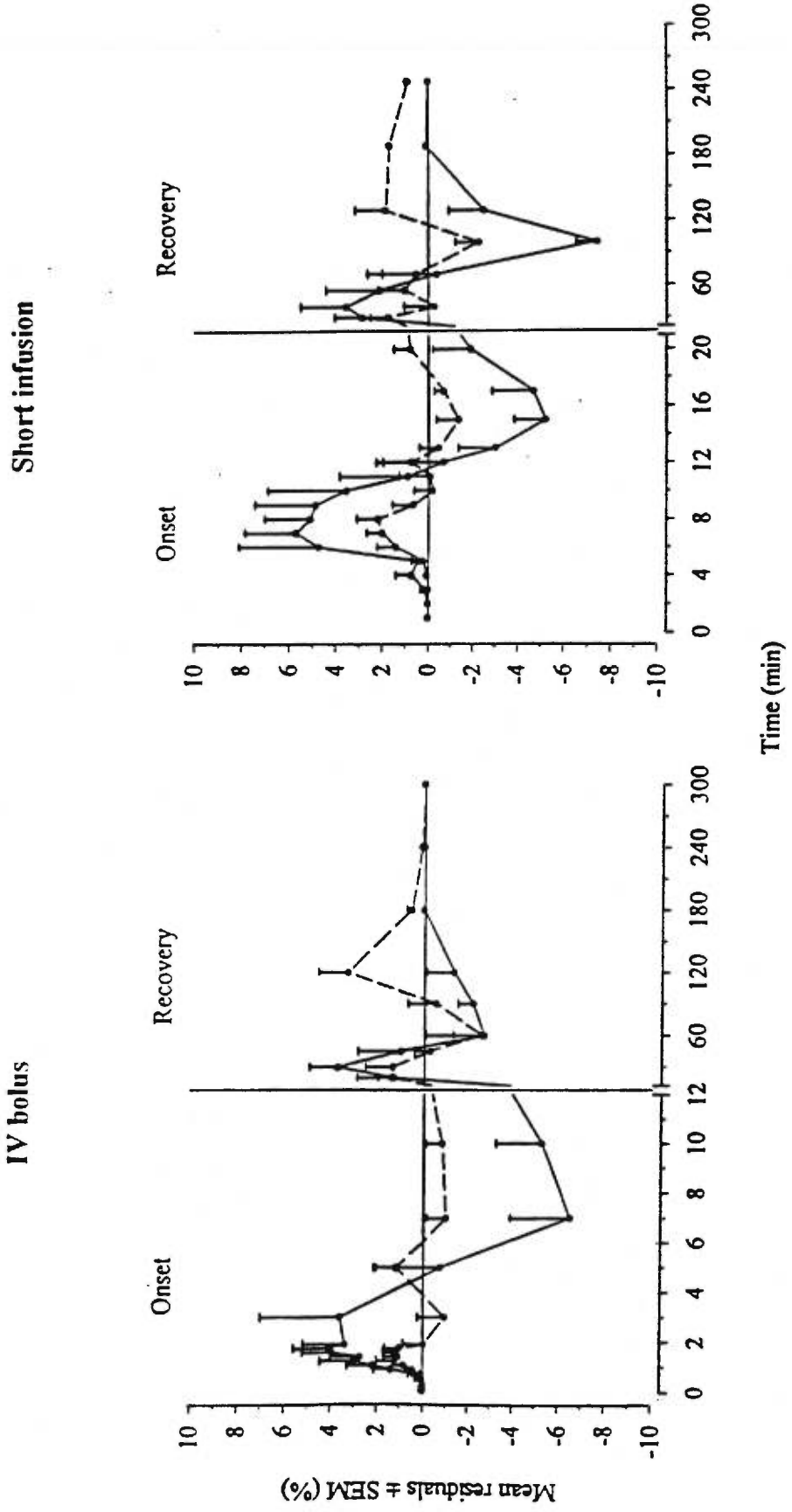

IV bolus
Short infusion
a
e
b
f
c
g
d
h
Neuromuscular block (%)
Effect compartment concentration (ng/ml)
Doxacurium plasma concentration (ng/ml)
Time (min)
Doxacurium effect compartment concentration (ng/ml)
Experimental data during onset
Experimental data during recov
Predicted curve with non parametric link model
Predicted curve with R_{tot} link model

FIGURE 3


IV bolus
Short infusion
Onset
Recovery
Onset
Recovery
Mean residuals ± SEM (%)
Time (min)
Simulation from non parametric link model
Simulation from R_{tol} link model

DISCUSSION

In anesthesia, the clinical pharmacokinetics and pharmacodynamics of non-depolarizing neuromuscular blockers have been used mainly to predict their duration of action (time until recovery from neuromuscular block) rather than their speed of onset (time until maximum block). However, a fast onset is crucial to rapidly intubate the patient and avoid pulmonary aspiration of gastric contents. Pharmacokinetic-pharmacodynamic (PK-PD) modeling can account for the delay between injection of the drug and maximum effect. It assumes that transfer of drug between the central compartment and the effect compartment takes time, and that the effect compartment concentration for a given effect is the same during onset and recovery.

Because onset is more rapid than recovery, fewer blood samples are taken during onset. As a result, the number of plasma concentration data-points used for the PK-PD modeling is usually higher during the recovery phase than during onset (Lebrault et al, 1985; 1986; Sohn et al, 1986)

Since parameters describing the PK-PD relationship are usually derived from a sigmoidal curve fitted through pooled onset and recovery data. A preponderance of data points during one phase could influence the sigmoid Emax modeling (Emax being the maximum possible effect that can be attributed to the drug) at the expense of the other phase. To avoid this problem, some investigators prefer to administer the muscle relaxant as a short infusion so more data-points can be

obtained during the onset of block (Cronnely et al, 1983; Rupp et al, 1987; Shanks et al, 1987). However, neuromuscular blocking agents are usually administered as bolus injections. The parameters derived with short infusion might not be applicable because of circulation delays before intravascular mixing (Chiou, 1989). Similarly, pharmacokinetic-pharmacodynamic relationships might be altered. The number of data-points collected during onset can be improved by extensive arterial blood sampling shortly after the bolus administration (every 10 seconds during the first 2 minutes) (Ducharme et al, 1993). By using this sampling technique, the initial plasma concentration-time profile could be precisely determined, and the sigmoidal curve can fit equally between onset and recovery phase.

The Rtot model used in this study, with a finite concentration of receptors in the effect compartment, is conceptually similar to the threshold model developed by Parker and Hunter (1992). In contrast to Parker and Hunter, who measured venous levels, we used arterial concentrations. With our method (Donati & Meistelman, 1991), the effect compartment, by virtue of its high receptor density, is considered a significant drain for drug molecules. This is consistent with experimental results at the frog motor endplate (Law Min et al, 1992), where buffered diffusion of the relaxant by the high density of nicotinic cholinergic receptors was found to be an important factor determining their speed of action. The mean receptor concentration obtained in this study corresponds to the estimates of receptor density in the synaptic cleft (Donati & Meistelman, 1991).

In this study, doxacurium PK-PD modeling was performed noncompartmentally, with a Keo estimation independent of any pharmacokinetic model or plasma concentration-effect function (Unadkat et al, 1989). Such a method has been validated for bolus doses of vecuronium and atracurium (Ducharme et al, 1993; 1994).The validity of this approach relies on frequent measurements of plasma concentrations until maximum block. In this experiment, the uninterrupted collection of 12 blood samples over the first 2 minutes provided an accurate description of the early kinetics following the doxacurium injection. Thus, the sigmoid curve covering both onset and recovery could be constructed with an equal number of data points from each phase, with 6 to 8 points between 20 and 80% block. Therefore, there was no predominant effect of one phase at the expense of the other.

The same time delay before peak arterial concentrations was also observed for vecuronium and atracurium. Since all these three drugs are charged, water soluble molecules, their volume of distribution is limited, with a similar Vdss of 0.137, 0.146 and 0.159, respectively. Blood flow or cardiac output are not limiting factors to the early distribution of polar drug, as opposed to lipid-soluble drugs like thiopental (Henthor et al, 1989). Since doxacurium, atracurium and vecuronium are bulky molecules with high molecular weights (1130, 928 and 558, respectively), their distribution from intravascular space into tissue may be rate-limiting. Because a 30 seconds time delay appears attributable to

intravascular mixing, one could take into account the diffusibility of the molecules, in view of the relatively slow onset of action of these drugs.

In conclusion, this clinical study represents the first attempt to compare the impact of input rate into the central compartment, ie bolus injection vs short infusion, on K_{eo} estimation. In addition, this is the first study to characterize doxacurium "early" pharmacokinetics using an extensive blood sampling procedure during the intravascular mixing. No difference in doxacurium K_{eo} values was found between both modes of iv administration, which suggests that K_{eo} is not influenced by the rate of input into the central compartment.

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APPENDIX I

EQUATIONS USED TO ESTIMATE THE PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

1. Two-compartment model with intravenous bolus injection (Gibaldi et al Perrier, 1982)

Plasma concentration (Cp):

$$Cp = Ae^{-\alpha t} + Be^{-\beta t}$$

Cp = Plasma concentration at time t

A = The zero - time intercept obtained by extrapolation of the distribution linear phase to t = 0

B = The zero - time intercept obtained by extrapolation of the elimination linear phase to t = 0

α = Complex constant corresponding to distribution phase

β = Complex constant corresponding to elimination phase

t = time

Distribution half-life ($t_{1/2\alpha}$):

$$(t_{1/2\alpha}) = 0.693/\alpha$$

Elimination half-life ($t_{1/2\beta}$):

$$(t_{1/2\beta}) = 0.693/\beta$$

Area under the time-plasma concentration curve (AUC):

$$AUC = A / \alpha + B / \beta$$

Area under the first moment of time-plasma concentration curve (AUMC):

$$AUMC = A / \alpha^2 + B / \beta^2$$

Mean resident time (MRT):

$$MRT = AUMC / AUC$$

Total clearance (CL):

$$CL = Dose / AUC$$

Volume of central compartment (Vc):

$$Vc = Dose / A + B$$

Appearant distribution volume (Vd_{area}):

$$Vd_{area} = Dose / AUC \times \beta$$

Volume of distribution at steady state (Vdss):

$$Vdss = CL \times MRT$$

2. Description of drug concentration at effect compartment (Ce) (Holford et Sheiner, 1981)

$$Ce = \frac{D \times Keo}{Vc} \times \frac{(K_{21} - \alpha) \times e^{-\alpha t}}{(\beta - \alpha) \times (K_{eo} - \alpha)} + \frac{(K_{21} - \beta) \times e^{-\beta t}}{(\alpha - \beta) \times (K_{eo} - \alpha)} + \frac{(K_{21} - K_{eo}) \times e^{-Keot}}{(\alpha - K_{eo}) \times (\beta - K_{eo})}$$

D = Dose

Keo = Elimination constant of effect compartment

K21 = Transfer constant from compartment 2 to compartment 1

t = time

3. Hill equation served to describe the sigmoid Emax model (Holford et Sheiner, 1981)

$$E_t = \frac{E_{max} \times Ce(t)^{\gamma}}{Ce_{50}^{\gamma} + Ce(t)^{\gamma}}$$

E_t = Effect at time t

E_{max} = Maximal effect

Ce(t) = Drug concentration in effect compartment at time t

Ce_{50} = Drug concentration in effect compartment at 50% maximal effect

$^{\gamma}$ = time