

REVIEW ARTICLE

Lawrence J. Saidman, M.D., Editor

Anesthesiology
61:444-453, 1984

Clinical Pharmacology of Vecuronium and Atracurium

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Summary

VECURONIUM (Norcuron™, ORG NC45) and Atracurium (Tracrium™, BW 33A) are two new nondepolarizing neuromuscular blocking drugs that have durations of action between those of succinylcholine and pancuronium. Although part of the developmental pharmacology has been described previously,^{1,2} the complete clinical pharmacology, which provided the basis for approval of these two drugs by the U. S. Food and Drug Administration, has not been summarized. Vecuronium and atracurium will be compared with three

other neuromuscular blocking drugs, succinylcholine, pancuronium, and *d*-tubocurarine.

Developmental Chemistry

Savage *et al.*³ are responsible for the manipulation of the steroid nucleus that resulted in the development of many neuromuscular blocking drugs, the most successful being the bisquaternary pancuronium (fig. 1). To provide a nondepolarizing neuromuscular blocker with a more rapid onset of action and shorter duration of action than that of pancuronium, the monoquaternary vecuronium was developed. Two nitrogen atoms are required for both neuromuscular blockers to retain potency. Also, the acetylcholine fragments in the ring D of both pancuronium and vecuronium make them among the most potent of all the steroid muscle relaxants studied³ (fig. 1). This rigid-trapped fragment probably interacts with the nicotinic cholinergic receptor and must have a low affinity for muscarinic receptors. Although both vecuronium and pancuronium are hydrophilic, vecuronium is slightly more lipophilic because it is a monoquaternary rather than bisquaternary compound. Because of this increased lipophilicity, vecuronium was predicted to have a different pharmacokinetic and pharmacodynamic profile than pancuronium,³ as described in the pharmacokinetic section below. Increased lipophilicity should enhance penetration of membranes and could alter vecuronium's route of elimination as compared with pancuronium, which proved to be the case.

Stenlake *et al.*⁴ used a different principle in developing a neuromuscular blocking drug having a short duration of action. Basically, the duration of action could be short if the neuromuscular blocking drug spontaneously degraded to inactive breakdown products. Thus, atracurium was developed. This quaternary ammonium compound breaks down in the absence of plasma enzymes through Hofmann elimination and to a lesser extent ester hydrolysis (fig. 2). Hofmann elimination is a nonbiologic method of degradation that occurs at a physiologic temperature and pH. By lowering temperature

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Received from the Department of Anesthesia, University of California, School of Medicine, San Francisco, California. Accepted for publication April 11, 1984.

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and pH, the rate of this reaction is decreased. Ester hydrolysis does not require pseudocholinesterase and is facilitated by an acid pH. The major breakdown products are laudanosine and a related quaternary acid, neither of which has neuromuscular blocking effects.⁵

Potency

The potency of vecuronium is equal to or slightly greater than that of pancuronium; the ratio of their potencies range from 1.0 to 1.74.⁶⁻¹³ Atracurium is less potent than pancuronium, the ratios of their potencies ranging from 0.25 to 0.33.¹³⁻¹⁵

When dose-response curves are constructed, the ED₉₀ or ED₉₅ (i.e., the doses of neuromuscular blocking drug that depress twitch tension 90% or 95%) can be derived. This dose usually provides adequate relaxation in an anesthetized patient. There is no significant clinical difference between the ED₉₀ and ED₉₅, but unfortunately investigators were not uniform in which values were reported. Thus, to compare the work of all investigators, both the ED₉₀ and ED₉₅ must be reported by us. However, the ED₉₀ or ED₉₅ varies, depending on several factors, including the anesthetic and the method of peripheral nerve stimulation (e.g., single twitch tension, train-of-four). Thus, the ED₉₀s range from 0.023 to 0.044 mg · kg⁻¹ for vecuronium^{6,16} and from 0.10 to 0.25 mg · kg⁻¹ for atracurium.¹⁷⁻²⁰

The method of constructing a dose-response curve will alter the conclusions regarding short-acting drugs such as vecuronium and atracurium more than for longer-acting drugs such as pancuronium. The traditional method is to administer a single bolus of neuromuscular blocking drug and to quantify the resulting neuromuscular blockade. One dose is given to each patient. Another method that requires fewer patients is to determine "cumulative dose-response" curves. With this method, a small dose of neuromuscular blocking drug

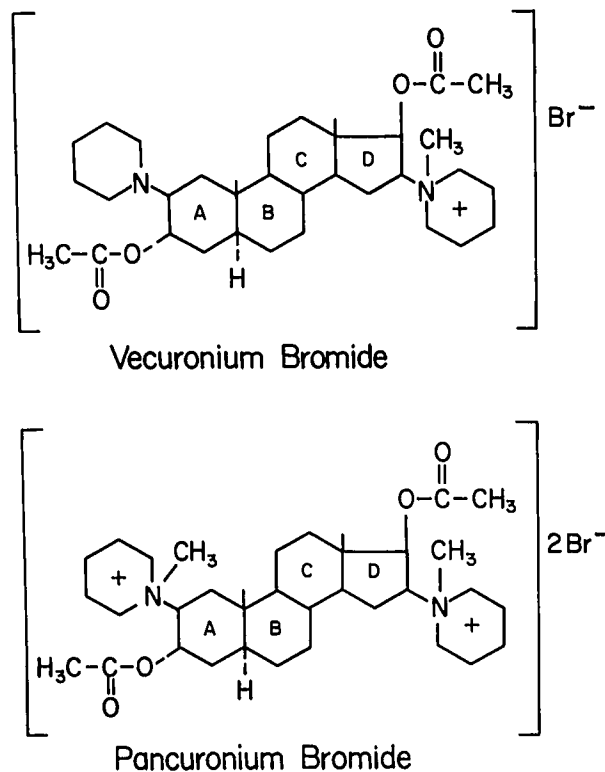
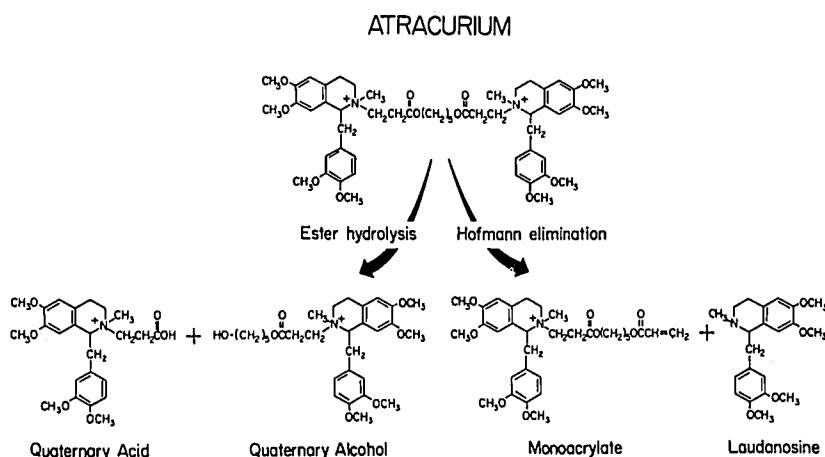


FIG. 1. Comparative chemical formulas for pancuronium and vecuronium.

is given and the resulting twitch depression observed. When no further change occurs for three or four twitches, an additional dose is given and its effect quantified. Additional doses of neuromuscular blocking drug are given until twitch height is depressed more than 90%. If three or four doses are given, then a complete dose-response curve can be constructed for each patient. For the longer-acting muscle relaxants, such as pancuronium, the single-bolus and cumulative

FIG. 2. Chemical formula for atracurium and its breakdown products that are formed from Hofmann elimination and ester hydrolysis.



method of constructing a dose-response curve produced essentially identical results.²¹ However, for vecuronium and atracurium, the cumulative dose-response method produced larger ED₉₀ values than did the single-bolus method.^{16,18,22} These shorter-acting drugs probably have larger ED₉₀ values when the cumulative method is used because much of the effect of the initial dose has dissipated before the last dose is given. Thus, the most accurate ED₉₀ for atracurium or vecuronium is that obtained with the single bolus method.

Onset Time and Duration of Action

The onset time (time from administration of muscle relaxant to its peak effect) and duration of action (time from administration of muscle relaxant to 90% or 95% recovery of control twitch tension) are similar for both vecuronium and atracurium.^{6-11,13-15,18-20,23-31} The doses of atracurium and vecuronium that depress twitch height less than 100% have onset times ranging from four to eight min. Because larger doses depress twitch tension 100%, onset time appears to be shorter. For example, four times the ED₉₅ of vecuronium has an onset time of 1.3 min²⁵. When three times the ED₉₅ of atracurium was given, onset times were 1.2¹⁴ and 1.3¹⁹ min. Despite markedly increasing the dose, neither vecuronium nor atracurium has an onset time as short as that of succinylcholine.³²

When equipotent doses are compared, both vecuronium and atracurium have a similar duration of action that is about one-third to one-half that of pancuronium.^{6,8,10,11,13,15,18,19} For doses depressing twitch tension less than 100%, duration of action is about 15-30 min.^{6,7,10,11,13,15,17,27,33} When three times the ED₉₅ of atracurium was given, duration of action was 76,¹⁵ 73,¹⁸ and 51¹⁴ min. When an approximately equipotent dose of vecuronium was given, duration of action was 53²⁷ and 60⁷ min. When a smaller dose of pancuronium (i.e., two times the ED₉₅) was given, the time from administration of muscle relaxant to only 25% recovery of control twitch tension was 158 min.³⁴

Not surprisingly, recovery time (time from 25% to 75% recovery of control twitch tension) was also shorter (30-50%^{6,8,11-13,35}) for vecuronium and atracurium than for pancuronium; these times ranged from 9 to 12 min for both atracurium and vecuronium.^{6-8,10,11,15,20,27,35}

Cumulative Effects

Both vecuronium and atracurium have little or no cumulative effects. The latter term often is confusing and misunderstood. Clinically, a lack of cumulative effect usually means that the duration of action of a given dose of neuromuscular blocking drug does not increase with repetitive doses. For example, Fahey *et*

*al.*⁶ administered a given dose of vecuronium to patients and observed its effect. When twitch tension had recovered to 25% of control, the same dose was given with the same resulting duration of action. The same duration of action from repetitive doses implies a lack of cumulative effects. Similar results were found by Buzello and Nöldge.³⁶ Ali *et al.*³⁷ observed a slight cumulative effect with vecuronium and no cumulative effect with atracurium.

Whether a neuromuscular blocking drug has a cumulative effect can be explained on a kinetic basis. With neuromuscular blockers that are not extensively metabolized (i.e., all blockers except succinylcholine and atracurium), recovery of neuromuscular function parallels the decrease in plasma concentration. Following a single dose of vecuronium or pancuronium, plasma concentration falls rapidly because of redistribution from the central to the peripheral compartment. With subsequent doses, muscle relaxant in the peripheral compartment limits this distribution phase, and the decrease in plasma concentration results from elimination or metabolism. Thus, both pancuronium, and to a lesser extent, vecuronium can be demonstrated to have cumulative effects. For atracurium, pharmacokinetic analyses reveal that there is not a distinct distribution phase with a rapid decrease in plasma concentration. Thus, recovery from the effects of atracurium depends predominantly upon elimination (in this case metabolism by Hofmann elimination and ester hydrolysis) rather than redistribution. As a result, recovery from the neuromuscular effects of atracurium is similar for the first and all subsequent doses.

Pharmacokinetics

Both vecuronium and atracurium have distinct pharmacokinetic properties as compared with currently used nondepolarizing muscle relaxants. For example, unlike pancuronium, metocurine, *d*-tubocurarine, or gallamine, neither vecuronium nor atracurium depends heavily on the kidney for elimination. Only 10-25% of an injected dose of vecuronium is excreted in the urine,³⁸⁻⁴⁰ the predominate route of elimination probably being the bile.³⁸ Although vecuronium should be metabolized into its 3-hydroxy, 17-hydroxy, and 3,17-hydroxy metabolites, as is pancuronium, only small amounts of these metabolites have been detected by methods such as thin-layer chromatography.³⁹ Although the precise extent to which vecuronium is metabolized has not been determined, apparently most of the drug excreted in the urine and bile is unchanged.³⁸ Further development of a sensitive assay distinguishing parent compound from its metabolites (e.g., mass spectrometry) may allow determination of the precise amount of vecuronium metabolized. How-

ever, these proposed metabolites have little or no cardiovascular or neuromuscular effects and, therefore, are of little concern.^{41,42} In humans, vecuronium has a more rapid clearance ($5.2 \pm 0.7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; mean \pm SD) and a shorter elimination half-life ($71 \pm 20 \text{ min}$) than pancuronium ($1.8 \pm 0.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $140 \pm 25 \text{ min}$).⁴³ These two characteristics probably account for the shorter duration of action of vecuronium.

Because atracurium is metabolized completely through Hofmann elimination and ester hydrolysis, it should not be excreted either in the urine or bile except in the form of a metabolite. Although urinary and biliary excretion has not been determined in humans, elimination half-life is about 20–30 min.^{44,45} Further confirmation of rapid metabolism is the rapid appearance of laudanosine in blood (*i.e.*, within 5–20 min).⁴⁴ Since laudanosine has no cardiovascular or neurologic effect when given in an iv dose of $4 \text{ mg} \cdot \text{kg}^{-1}$, its known convulsant effect probably occurs at blood levels unlikely to be achieved by prolonged atracurium administration.⁴⁶ The dose (laudanosine)–response (convulsions) and blood levels of laudanosine required to produce convulsions has not been determined precisely. Furthermore, the extent to which laudanosine is formed with prolonged administration of atracurium has not been determined.

Even though atracurium and vecuronium produce neuromuscular blockade of similar duration, calculated values for their pharmacokinetic variables are quite different. For example, elimination half-life is about 22 min for atracurium and 71 min for vecuronium.^{43,46}

The interrelationship between pharmacokinetic variables and neuromuscular blockade clearly differs for these drugs (fig. 3). All previous pharmacokinetic models, including that for vecuronium, assumed that elimination of a drug occurs from only one compartment. This approach is inappropriate for atracurium, because Hofmann elimination can occur from all body compartments. A pharmacokinetic model that accounts for multicompartmental elimination has not been developed.

Factors that Influence the Pharmacokinetics or Pharmacodynamics of Vecuronium and Atracurium

ANESTHESIA

Anesthetics enhance a nondepolarizing neuromuscular blockade in the following order: nitrous oxide–narcotics < halothane < isoflurane and enflurane.⁴⁷ The potencies of atracurium and vecuronium appear to be influenced less by the choice and concentration of anesthetic than are the potencies of *d*-tubocurarine and pancuronium. Enflurane and isoflurane augment a *d*-tubocurarine and pancuronium neuromuscular blockade about twice as much as does an equipotent concentration of

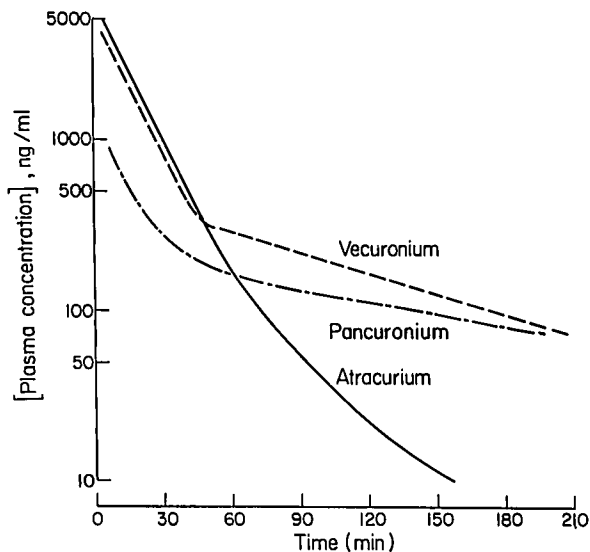


FIG. 3. Comparison of typical plasma decay curves from vecuronium, 0.28 mg/kg iv, pancuronium, 0.05 mg/kg, and atracurium, 0.5 mg/kg. Note that the peak plasma concentration of pancuronium is much lower because a smaller dose had been given (data taken from Fahey *et al.*^{40,44}).

halothane^{48–50} (fig. 4). For example, the ED₅₀s of *d*-tubocurarine and pancuronium are 1.70 and 0.27 mg/m², respectively, during isoflurane anesthesia and 5.60 and 0.49 mg/m², respectively, during halothane anesthesia.^{49,50} In contrast, the augmentation of a vecuro-

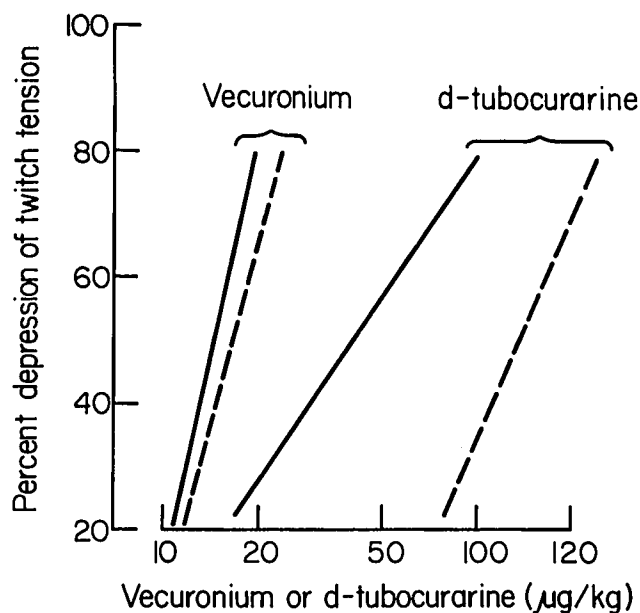


FIG. 4. Comparison of dose response curves of *d*-tubocurarine and vecuronium during isoflurane (—) and halothane (---) anesthesia (1.2 MAC concentration). Note that the difference between halothane and isoflurane is more with *d*-tubocurarine than it is with vecuronium (data taken from Miller *et al.*⁴⁹ and Rupp *et al.*²⁸).

nium- or atracurium-induced neuromuscular blockade by enflurane and isoflurane is only 20–30% greater than the augmentation produced by halothane or nitrous oxide–narcotic anesthesia^{17,26,28,51,52} (fig. 4).

Changes in the end-tidal concentration of inhaled anesthetics also have a lesser influence on neuromuscular blockades produced by vecuronium or atracurium than those produced by other nondepolarizing neuromuscular blockers. Increasing the anesthetic concentration from 1.2 MAC to 2.2 MAC decreases the ED₅₀ of vecuronium 51%, 33%, and 18% during enflurane, isoflurane, and halothane anesthesia, respectively.²⁸ Yet, the ED₅₀s of *d*-tubocurarine and pancuronium decreased 62% and 57%, respectively, for similar increases in the halothane concentration, and 30% and 70%, respectively, for similar increases in the isoflurane concentration.⁵⁴

The reasons for vecuronium and atracurium being less influenced by the specific anesthetic and its dose or concentration are unknown.

AGE

Infants and Children: Comparing data from pediatric studies with those from adult studies sometimes is difficult because of differing experimental conditions and methods, such as depth of anesthesia, method of nerve stimulation, and method of constructing dose–response curves (single-bolus *vs.* cumulative). Despite these limitations, certain conclusions can be made cautiously.

The potency of both vecuronium and atracurium are similar in pediatric and adult patients. During halothane and nitrous oxide anesthesia, the ED₅₀ of vecuronium was 16.5 μg/kg in infants (<one year), 19.0 μg/kg for children (1–8 years), and 15.0 μg/kg for adults.⁵⁵ Goudsouzian *et al.*⁵⁶ found ED₅₀ values of 33 μg/kg and 23 μg/kg for children (2–9 years) and adolescents (10–17 years), respectively. The higher ED₅₀ values in the latter study may be partly explained by the use of the cumulative method for producing dose–response curves.²² Although Brandom *et al.*⁵⁷ found a larger ED₅₀ value in children, the differences were small. Specifically, the ED₅₀ values were 85, 132, and 101 μg/kg for infants, children, and adolescents, respectively.^{57,58} Goudsouzian *et al.*⁵⁹ found the ED₅₀ of atracurium to be 110 μg/kg for children and 120 μg/kg for adolescents. Interestingly, when Brandom *et al.*^{57,58} recalculated their data on a surface-area basis, the ED₅₀ values were 1,600, 3,266, and 3,338 μg/m² for infants, children, and adolescents, respectively. This technique corrects for age-related changes in extracellular fluid volume (*i.e.*, the volume of distribution of neuromuscular blocking drugs). Thus, as is the case with *d*-tubocurarine, neuromuscular blockade may occur at a lower plasma concentration of atracurium in infants than in children and adolescents.⁶⁰

The duration of a neuromuscular blockade induced

by vecuronium (70 μg/kg) appears to be longer in infants (73 ± 27 min) than in children (35 ± 6 min) or adults (53 ± 7 min).⁵⁵ Goudsouzian *et al.*⁵⁶ did not study infants but found similar durations of action in children and adolescents. Conversely, the duration of atracurium's action is not prolonged in infants.^{57,58,61} This difference between vecuronium and atracurium in infants may be related to the distinctive pharmacokinetic characteristics of each drug. With a larger volume of distribution in infants, more vecuronium (and *d*-tubocurarine⁶⁰) would be in the peripheral compartment, inaccessible to the organs of clearance. Also, age-related changes in biliary clearance may account for vecuronium's longer duration of action in infants. For atracurium, the unusual pathways of elimination (Hofmann elimination and ester hydrolysis) result in its destruction in both the peripheral and central compartments. Thus, the duration of atracurium's action may depend less upon these age-related differences in organ function or volume of distribution.

The Elderly: d'Hollander *et al.*^{62–64} found that a difference existed between vecuronium and atracurium in the elderly. Less vecuronium was required to sustain a steady state of paralysis, and recovery from neuromuscular blockade was longer in elderly patients (>60 years) than in younger patients,⁶² yet, this same group found no age-related changes associated with atracurium.⁶⁴ This is the only study with atracurium in the elderly.

Rupp *et al.*⁶⁵ performed a pharmacokinetic and pharmacodynamic study with vecuronium in elderly patients (>70 years). The plasma concentration of vecuronium required to depress twitch height 50% did not change with age. Conversely, plasma clearance and the volume of distribution decreased in the elderly, probably because of decreased extracellular fluid and muscle mass. However, elimination half-life did not change in the elderly, suggesting that neuromuscular blockade should not be prolonged in the elderly. This contrasts with the results of d'Hollander *et al.*⁶² Obviously, more study is required to better define the influence of age on the neuromuscular blockades produced by vecuronium and atracurium.

SUCCINYLCHOLINE

Prior administration of succinylcholine probably enhances the neuromuscular blockades from vecuronium and atracurium.^{11,53,66} However, as with pancuronium^{67,68} and *d*-tubocurarine,^{69,70} there is lack of agreement among various investigators. Stirt *et al.*⁵³ found that prior administration of succinylcholine, 1.0 mg/kg, increased the intensity of the atracurium neuromuscular blockade from 52% to 84% but did not increase its duration. d'Hollander *et al.*⁷¹ found that succinylcholine augmented both the magnitude and duration of a vecuronium-induced neuromuscular blockade. This aug-

mentation would occur if vecuronium had been given within 30 min of succinylcholine administration. Krieg *et al.*⁶⁶ found that vecuronium given after succinylcholine caused a 19% greater depression of twitch tension than did vecuronium given without a prior dose of succinylcholine. Yet, Fisher and Miller⁷² found that prior administration of succinylcholine did not alter a vecuronium-induced neuromuscular blockade. Clearly, the response to vecuronium, and probably atracurium, varies when given after succinylcholine.

ACID-BASE BALANCE

In cats, Funk *et al.*⁷³ found that acidosis augmented and alkalosis lessened a vecuronium-induced neuromuscular blockade. In humans, Gencarelli *et al.*⁷⁴ found that the timing of changes in end-tidal P_{CO_2} was important as to its influence on vecuronium. During an end-tidal P_{CO_2} of 25, 41, or 56 mmHg, neither the magnitude nor recovery time from a vecuronium-induced neuromuscular blockade changed. However, when vecuronium was infused at a constant rate and then the end-tidal P_{CO_2} was changed, respiratory acidosis augmented and respiratory alkalosis lessened twitch tension. Thus, if respiratory acidosis occurs during a vecuronium-induced neuromuscular blockade, an augmented and prolonged blockade may result.

The influence of changes in acid-base balance on an atracurium-induced neuromuscular blockade has not been studied in humans. In an *in vivo* cat preparation, respiratory and metabolic acidosis augmented and respiratory and metabolic alkalosis lessened an atracurium neuromuscular blockade.⁷⁵

Cardiovascular Effects

The two major cardiovascular effects from older nondepolarizing blockers are tachycardia from vagal blockade (*e.g.*, pancuronium and gallamine) and hypotension from histamine release (*e.g.*, *d*-tubocurarine and metocurine). In contrast, vecuronium and, in large part, atracurium have little or no cardiovascular effects. For example, Booi *et al.*⁷⁶ gave three times the ED_{90} of vecuronium *iv* to dogs and found no change in heart rate, blood pressure, and cardiac output. Marshall *et al.*⁷ found that doses of vecuronium up to 20 times greater than those required for neuromuscular blockade produced no cardiovascular changes in cats and dogs. Furthermore, the proposed metabolites essentially were free of cardiovascular effects.⁴¹ Lastly, vecuronium does not release histamine.⁷⁸

Gregoretti *et al.*⁷⁹ administered vecuronium, 0.1 mg/kg *iv*, to patients anesthetized with enflurane and halothane. The only cardiovascular change was a slight decrease in heart rate (from 76 bpm to 63 bpm) during

halothane anesthesia. However, the control heart rate was obtained before both vecuronium and halothane were administered. The investigators concluded that when vecuronium is used, its lack of vagolytic activity may allow drug- or reflex-induced bradycardia to occur more easily during surgery and anesthesia. Yet, Engbaek *et al.*⁸⁰ found no change in heart rate, arterial blood pressures, or systolic time intervals from vecuronium, 57 μ g/kg *iv*, in patients also anesthetized with halothane. To severely test vecuronium's apparent lack of cardiovascular effects, Morris *et al.*⁸¹ gave 0.28 mg/kg (12 times the ED_{90}) of vecuronium *iv* to patients anesthetized with halothane who were about to undergo coronary artery bypass grafting. Heart rate and arterial blood pressure did not change. Cardiac output decreased 9% and systemic vascular resistance decreased 12%.

Atracurium does cause release of histamine but in amounts less than those produced by metocurine or *d*-tubocurarine.⁸² Accordingly, when doses of atracurium up to 0.4 mg/kg *iv* were given, no significant change (<5% of control) in arterial blood pressure or heart rate occurred during various anesthetic techniques.^{17-20,83} Occasionally these doses were associated with flushing.^{58,59} Larger doses of atracurium ranging from 0.5 mg/kg to 1.0 mg/kg have been associated with a typical histamine-like cardiovascular response, including hypotension and tachycardia. For example, Basta *et al.*¹⁵ noted that arterial blood pressure decreased 13% and 20% from control after administration of atracurium, 0.5 mg/kg and 0.6 mg/kg *iv*. Heart rate increased to 105% and 108% of control, respectively. These changes were associated with slight facial flushing. Pokar and Brandt⁸⁴ administered atracurium, 0.6-1.0 mg/kg, into right atrial catheters in patients who had undergone coronary artery bypass surgery. Four of nine patients had a decrease of more than 10% (maximum 17%) in arterial blood pressure. We conclude that doses less than 0.6 mg/kg rarely are associated with cardiovascular changes. Larger doses can cause a transient histamine response, but less than that associated with *d*-tubocurarine or metocurine.

Antagonism

There have been no reports of difficulty in antagonizing either a vecuronium- or atracurium-induced neuromuscular blockade with anticholinesterase drugs. Basta *et al.*¹⁵ found that the doses of neostigmine required to antagonize neuromuscular blockade produced by atracurium and metocurine were similar. Also, the times from administration of neostigmine to recovery of 98% control twitch height were similar: 8.2 min for atracurium and 7.6 min for metocurine. Conversely, Fahey *et al.*⁶ found that less neostigmine was required to antagonize a neuromuscular blockade induced by vecuronium

than one induced by pancuronium. However, this conclusion was based on data obtained from administration of intermittent boluses of neostigmine. Possibly because a neuromuscular blockade by vecuronium would terminate spontaneously more rapidly than one by pancuronium, less neostigmine would be required with vecuronium. To compensate for the possibility that this pharmacokinetic characteristic would lessen the neostigmine requirement, Gencarelli and Miller⁸⁵ continuously infused either pancuronium or vecuronium and found no difference in the neostigmine dose required for antagonism. They concluded that vecuronium and pancuronium effectively and equally (independent of their pharmacokinetics) are antagonized by neostigmine. Baird *et al.*⁸⁶ found that edrophonium, 0.5–1.0 mg/kg iv, rapidly (*i.e.*, 1–2 min) restored a vecuronium depressed twitch to 80% (*i.e.*, 20% depression of twitch tension still remaining) of the control height but that an additional 6 to 8 minutes was required for complete restoration of neuromuscular function, as judged by the train-of-four response.

These studies indicate that both vecuronium- and atracurium-induced neuromuscular blockades are antagonized readily by edrophonium and neostigmine. Because the new neuromuscular blocking drugs produce a blockade of relatively short duration, an antagonist may not be necessary. For example, Katz *et al.*¹⁸ found it necessary to antagonize only five of 25 neuromuscular blockades from atracurium. Undoubtedly, administration of an antagonist is not always necessary. However, we believe spontaneous recovery should not be relied upon for termination of neuromuscular blockade unless a sustained response to a tetanic stimulus of 100 Hz for 5 s or a completely normal train-of-four unquestionably exists.

Special Clinical Situations

CARDIAC SURGERY AND CARDIOPULMONARY BYPASS

Because they have little or no cardiovascular effects, vecuronium and atracurium may be appropriate neuromuscular blocking drugs for cardiac surgery.^{81,84,87} Very large doses of vecuronium (*e.g.*, 0.28 mg/kg) can be given with no cardiovascular effects. However, large doses of atracurium may cause hypotension.⁸⁴ For example, when atracurium, 0.3 mg/kg, was given to eight patients about to undergo elective coronary artery surgery, one patient had a decrease in mean arterial pressure (from 70 to 55 mmHg) and other signs consistent with histamine release.⁸⁷ Perhaps prior diuretic therapy made these patients more susceptible to even the slight histamine release associated with atracurium administration.

The lack of cardiovascular effects associated with large doses of vecuronium can be a disadvantage when the high-dose fentanyl approach to anesthesia is used.

Pancuronium is commonly used: its vagolytic effect counteracts the tendency of fentanyl to produce bradycardia. Thus, when vecuronium is given with high-dose fentanyl anesthesia (especially cardiac anesthesia) heart rate often decreases.⁸⁸

Hypothermia and cardiopulmonary bypass also can affect the amount of atracurium or vecuronium required for neuromuscular blockade. Flynn *et al.*⁸⁹ found that 43% less atracurium was required to maintain a 90–95% neuromuscular blockade during hypothermic cardiopulmonary bypass. They attributed the apparent increased potency of atracurium to the fact that hypothermia reduced the rate of Hofmann degradation. Buzello *et al.*⁹⁰ compared pancuronium and vecuronium before and after cardiopulmonary bypass. Before bypass pancuronium acted about two times longer than vecuronium. However, during hypothermic bypass, the durations of action of pancuronium and vecuronium increased 1.8-fold and fivefold, respectively. Thus, during hypothermic bypass, pancuronium and vecuronium had similar durations of action. Consequently, we conclude that hypothermic cardiopulmonary bypass is associated with a marked increase in the duration of neuromuscular blockade from both atracurium and vecuronium.

OBSTETRICS

Both vecuronium and atracurium have been successfully used in patients undergoing cesarean section. Baraka *et al.*⁹¹ gave vecuronium, 0.05 mg/kg, to patients undergoing cesarean section after recovery from an initial dose of succinylcholine had occurred. The mean duration of neuromuscular blockade was 19 min. Furthermore, Apgar scores did not differ for infants delivered before vecuronium administration ($n = 9$) and those delivered after vecuronium administration ($n = 19$). Dailey *et al.*⁹² confirmed that vecuronium had difficulty crossing the placental barrier. Specifically, when a 0.04 mg/kg dose of vecuronium or pancuronium was given to the mother, 8.5–26.4 ng/ml and 12.2–34.2 ng/ml, respectively, of drug was found in umbilical-cord venous blood. The ratio of the drug concentration in umbilical-cord venous blood to that in maternal venous blood was 0.11 for vecuronium and 0.19 for pancuronium. In a similar study, Demetriou *et al.*⁹³ also found a ratio of 0.11 for vecuronium. Lastly, plasma clearance of vecuronium is more rapid in pregnant patients, probably because of cardiovascular and fluid shifts during pregnancy.⁹² Although the increased clearance rate during pregnancy would presumably result in a shorter neuromuscular blockade, this assumption has not been verified.

Frank *et al.*⁹⁴ also successfully used atracurium in patients undergoing cesarean section. In five of 26 patients, atracurium levels in maternal blood ranged from 0.7 $\mu\text{g/ml}$ to 3.3 $\mu\text{g/ml}$ 3 min after drug administration. Concentrations in umbilical-cord venous blood

were too small to detect ($<0.23 \mu\text{g/ml}$). Perhaps a more sensitive assay similar to that of Fahey *et al.*⁴⁴ (sensitivity to 10 ng/ml) would have been able to detect atracurium in such samples. Still, there is no reason to believe that highly ionized drugs such as vecuronium or atracurium would cross the placental barrier in significant amounts.

RENAL DISEASE

Because neither vecuronium nor atracurium depend heavily on the kidney for their elimination, duration of neuromuscular blockade should not be prolonged in patients with renal failure. This conclusion indeed has been confirmed with large doses of atracurium (0.5–2.3 mg/kg)^{44,95} and vecuronium (0.28 mg/kg).⁴⁰ Thus, vecuronium and atracurium are the only two currently used, nondepolarizing blocking drugs whose neuromuscular blockades are not prolonged by renal failure.

LIVER DISEASE

Because atracurium is metabolized through Hofmann elimination and ester hydrolysis, its pharmacokinetics and duration of neuromuscular blockade should not be altered by impaired hepatic function. Ward and Neill⁹⁶ determined the pharmacokinetics of atracurium in normal patients and in six patients with acute hepatic and renal failure. The values for pharmacokinetic variables did not differ for the two groups, plasma elimination half-life being 22 min for patients with hepatic and renal failure and 21 min for normal patients. Although duration of neuromuscular blockade was not measured, it presumably was not prolonged by hepatic failure.

Because vecuronium significantly is eliminated in the bile, one might predict that liver disease would prolong a vecuronium-induced neuromuscular blockade. After vecuronium, 0.2 mg/kg iv, was given to patients with cirrhosis, elimination half-life increased from 58 min to 84 min, and plasma clearance decreased 50%.^{**} Also, the duration of neuromuscular blockade increased from 62 min to 130 min.^{**} However, protein binding of vecuronium was not altered by the presence of cirrhosis.⁹⁷

We conclude that the duration of neuromuscular blockade produced by vecuronium, but *not* atracurium, will be increased in patients with impaired hepatic function.

Summary

Vecuronium and atracurium provide additional flexibility to the clinician using neuromuscular blocking drugs. The shorter duration of action, lack of significant

cardiovascular effects, and the lack of dependence on the kidney for elimination provide clinical advantages over, or alternatives to, currently available nondepolarizing neuromuscular blocking drugs.

We would like to thank Pauline Snider and Susan M. S. Ishida for their editorial help, and Dr. Robert B. Morris for his scientific advice, in the preparation of this manuscript.

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