Evaluations of New Drugs

Vecuronium: A New Nondepolarizing Neuromuscular-Blocking Agent

Clinical Pharmacology, Pharmacokinetics, Cardiovascular Effects and Use in Special Clinical Situations

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Vecuronium provides additional flexibility to the clinician using neuromuscular-blocking drugs. Its shorter duration of action, lack of significant cardiovascular effects and lack of dependence on the kidney for elimination provide clinical advantages over, or alternatives to, currently available, nondepolarizing neuromuscular-blocking drugs.
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OUTLINE

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Vecuronium (Norcuron, ORG NC45) is one of two new nondepolarizing neuromuscular-blocking drugs that have durations of action between those of succinylocholine and pancuronium; atracurium is the other new agent. Although part of the developmental pharmacology was described previously,[1,2] the complete clinical pharmacology of vecuronium has not been summarized. Vecuronium is compared with three other neuromuscular blocking drugs — succinylcholine, pancuronium and *d*-tubocurarine.

Developmental Chemistry

Savage et al[3] are responsible for the manipulation

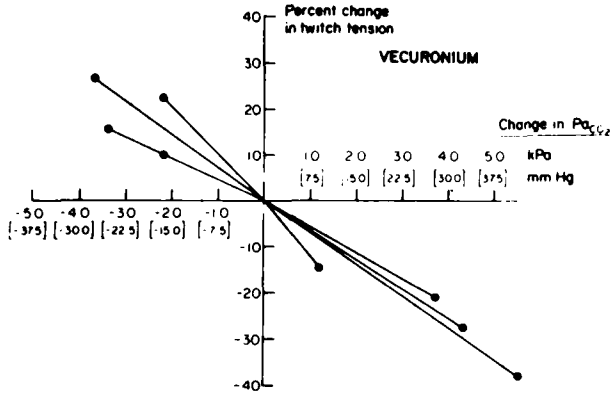


Figure 1. Comparative chemical formulas for pancuronium and vecuronium.

of the steroid nucleus that resulted in the development of many neuromuscular-blocking drugs, the most successful being the bisquaternary pancuronium (figure 1). To provide a nondepolarizing neuromuscular blocker with more rapid onset (which has proven not to be the case with vecuronium) and shorter duration of action than those of pancuronium, the monoquaternary vecuronium was developed. Two nitrogen atoms are required for both neuromuscular blockers to retain potency. Also, the acetylcholine fragments in ring D of both pancuronium and vecuronium make them among the most potent of all the steroid muscle relaxants studied.[3] This rigid-trapped fragment probably interacts with the nicotinic cholinergic receptor and must have a low affinity for muscarinic receptors. Also, to provide a blocker with little or no cardiovascular effects, the acetylcholine fragment at ring A in the steroid skeleton was altered. Although both vecuronium and pancuronium are hydrophilic, vecuronium may be slightly more lipophilic because it is a monoquaternary rather than bisquaternary compound. Because of this, vecuronium was predicted to have a different pharmacokinetic and pharmacodynamic profile than pancuronium.[3]

Potency

The potency of vecuronium is equal to or slightly greater than that of pancuronium; the ratio of their potencies ranges from 1.0–1.74.[4–11] When dose-response curves are constructed, the ED_{90} or ED_{95} (dose of neuromuscular blocking drug that depresses twitch tension 90% or 95%) can be derived. This dose usually provides adequate relaxation in an anesthetized patient. However, the ED_{90} or ED_{95} varies depending on several factors, including the anesthetic and method of peripheral nerve stimulation (e.g., single twitch tension, train-of-four). Thus the ED_{90} ranges from 0.023–0.44 mg·kg^{-1} for vecuronium.[4, 12]

The method of constructing a dose-response curve alters the conclusions regarding short-acting drugs such as vecuronium more than for longer-acting agents 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 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 of four doses are given, 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 methods of constructing a dose-response curve produced essentially identical results.[13] For vecuronium, however, the cumulative dose-response method produced larger ED_{90} values.[12, 14] Vecuronium probably has a larger ED_{90} value when the cumulative method is used because much of the effect of the initial dose has dissipated before the last dose is given.

Onset Time and Duration of Action

The doses of vecuronium that depress twitch height less than 100% have onset times (time from administration of muscle relaxant to its peak effect) ranging from 4–8 minutes (Table 1).[4-9, 11, 15-21] Because larger doses depress twitch tension 100%, onset time appears to be shorter. For example, four times the ED_{95} of vecuronium has an onset time of 1.3 minutes.[17] Despite markedly increasing the dose, vecuronium never has an onset time as short as that of succinylcholine.

Vecuronium has a duration of action (time from vecuronium administration to 90% or 95% recovery of control twitch tension) that is about 50–67%

Table 1. Time Course of Action of Vecuronium

Dose (mg/kg)	Onset Time (min)	% Depression of Twitch Tension	Duration (min)
0.01	6.7	25	14
0.014	6.3	36	16
0.02	6.0	76	27
0.07	3.8	100	34
0.14	2.8	100	104

From reference 4.

Table 2. Comparative Pharmacokinetics of Vecuronium and Pancuronium in Anesthetized Humans

Drug	Renal Function	Half-life–α (min)	Half-life–β (min)	$V_{D_{SS}}$ (ml/kg)	Clearance (ml/kg/min)
Vecuronium	Normal	8.5	80	194	3.0
Vecuronium	Absent	10.5	97	239	2.5
Pancuronium	Normal	20.0	140	260	1.8
Pancuronium	Absent	12.0	257	296	0.8

Half-life–α = distribution half-life; half-life–β = elimination half-life; $V_{D_{SS}}$ = volume of distribution at steady state. From references 26 and 29.

shorter than that of pancuronium.[4, 6, 8, 9, 11] For doses depressing twitch tension less than 100%, duration of action is about 15–30 minutes.[4, 5, 8, 9, 11, 19] When three times the ED_{95} of vecuronium was given, duration of action was 53[19] and 60[5] minutes. When a smaller dose of pancuronium (two times the ED_{95}) was given, the time from administration of muscle relaxant to only 25% recovery of control twitch tension was over 100 minutes.[4]

It is not surprising that recovery time (time from 25–75% recovery of control twitch tension) was also shorter (30–50%[4, 6, 9–11, 22]) for vecuronium than for pancuronium; these times ranged from 9–12 minutes for vecuronium.[4–6, 8, 9, 19, 22]

Cumulative Effects

The term "cumulative effect" is often 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. Vecuronium has little or no cumulative effect. Fahey et al[4] 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 duration of action. The same duration of action from repeated doses implies a lack of cumulative effects. Similar results were reported by Buzello and Nöldge.[23]

Whether or not a neuromuscular-blocking drug has a cumulative effect can be explained on a kinetic basis. Recovery of neuromuscular function parallels the decrease in plasma concentration. After 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 a drug that has a slow rate of elimination, such as pancuronium, has cumulative effects. When a drug has a more rapid rate of elimination, such as vecuronium, little or no cumulative effect occurs.

Pharmacokinetics

Vecuronium has distinct pharmacokinetic properties as compared to currently used nondepolarizing muscle relaxants. For example, unlike pancuronium, metocurine, *d*-tubocurarine or gallamine, vecuronium does not depend heavily on the kidney for its elimination. Only 10–25% of an injected dose of vecuronium is excreted in the urine,[24–26] the predominant route of elimination probably being the bile.[24] 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.[25] The precise extent to which vecuronium is metabolized has not been determined, but apparently most of the drug excreted in the urine and bile is unchanged.[24, 26] 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. These proposed metabolites have little or no cardiovascular or neuromuscular effects, however, and therefore are of little concern.[27, 28] In humans, vecuronium has a more rapid clearance (5.2 ± 0.7 $ml \cdot kg^{-1} \cdot min^{-1}$; mean ± SD) and a shorter elimination half-life (71 + 20 min) than pancuronium (1.8 ± 0.4 $ml \cdot kg^{-1} \cdot min^{-1}$; 140 ± 25 min)[29] (Table 2). Thus these two characteristics are probably due to rapid hepatic uptake and biliary excretion and probably account for the shorter duration of action of vecuronium.

Factors that Influence the Pharmacokinetics or Pharmacodynamics of Vecuronium

Anesthesia

Anesthetics enhance a nondepolarizing neuromuscular blockade in the following order: nitrous oxide-narcotics < halothane < isoflurane and enflurane.[30] The potency of vecuronium appears 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 neuromus-

cular blockade about twice as much as does an equipotent concentration of halothane (Figure 2).[31-33] For example, the ED_{50} of *d*-tubocurarine and pancuronium is 1.70 and 0.27 mg/m² respectively, during isoflurane anesthesia, and 5.60 and 0.49 mg/m² respectively, during halothane anesthesia.[32, 33] In contrast, the augmentation of a vecuronium-induced neuromuscular blockade by enflurane and isoflurane is only 20–30% greater than the augmentation produced by halothane or nitrous oxide-narcotic anesthesia (Figure 2).[18, 20, 34]

Changes in the end-tidal concentration of inhaled anesthetics also have less influence on neuromuscular blockades produced by vecuronium than those produced by other nondepolarizing neuromuscular blockers. Increasing the maximum anesthetic concentration (MAC) from 1.2 to 2.2 decreases the ED_{50} of vecuronium 51%, 33% and 18% during enflurane, isoflurane and halothane anesthesia respectively.[20] Yet the ED_{50} 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.[35]

The reasons for the potency and duration of action of vecuronium being less influenced by the choice of anesthetic and its dose or concentration are unknown.

Age

Infants and Children

Comparing data from pediatric studies with those from adult studies is sometimes difficult because of different 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 cautiously be made.

The potency of vecuronium is similar in pediatric and adult patients. During halothane and nitrous oxide anesthesia, the ED_{50} of vecuronium was 16.5 μg/kg in infants (< 1 year), 19.0 μg/kg for children (1–8 years) and 15.0 μg/kg for adults (Figure 3).[36] Goudsouzian et al[37] found ED_{50} values of 33 μg/kg and 23 μg/kg for children (2–9 years) and adolescents (10–17 years) respectively. The higher values in the latter study may be partly explained by the use of the cumulative method for producing dose-response curves.[14]

The duration of a neuromuscular blockade induced by vecuronium (70 μg/kg) appears to be long-

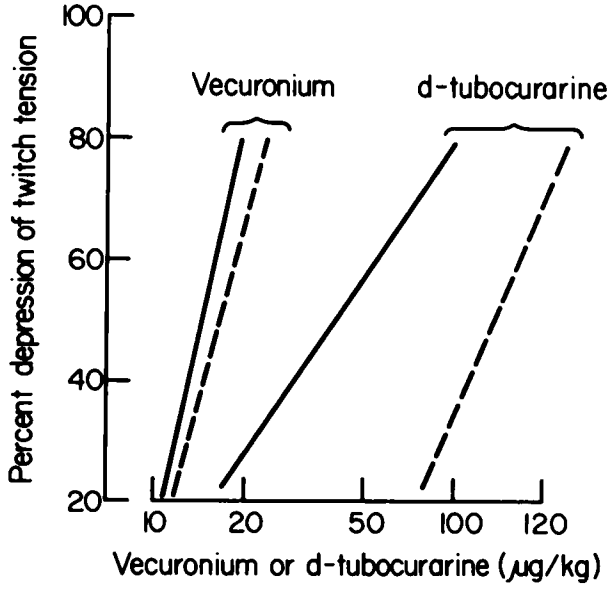


Figure 2. Comparison of dose-response curves of *d*-tubocurarine and vecuronium during isoflurane (___) and halothane (----) anesthesia (1.2 MAC concentration). Note that the difference between halothane and isoflurane is more with *d*-tubocurarine than it is with vecuronium. (Adapted from references 20 and 32).

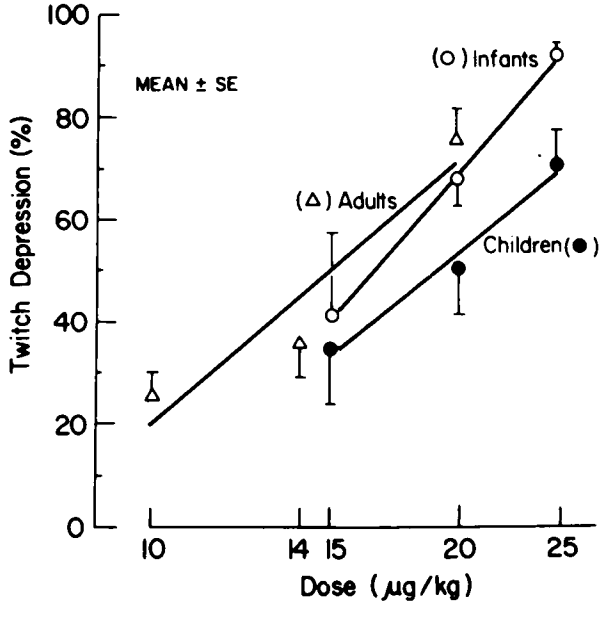


Figure 3. Dose-response curves for vecuronium for three age groups. Values for adults (from reference 4) were obtained under comparable anesthetic conditions. Mean and standard error for twitch depression for each dose are represented by vertical lines. (Reprinted with permission. From reference 36).

er in infants (73 ± 27 min) than in children (35 ± 6 min) or adults (53 ± 7 min).[36] Goudsouzian et al[37] did not study infants but noted similar durations of action in children and adolescents. The longer duration of action in infants may be explained on a pharmacokinetic basis. With a larger volume of distribution in infants, more vecuronium (and *d*-tubocurarine[38]) 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.

The Elderly

D'Hollander et al[39] noted that less vecuronium was required to sustain a steady state of paralysis, and recovery from neuromuscular blockade was longer in elderly (>60 years) than in younger patients. Rupp et al[40] performed a pharmacokinetic and dynamic 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. Elimination half-life did not change, however, suggesting that neuromuscular blockade should not be prolonged in the elderly. This contrasts with the results of d'Hollander et al.[39] Obviously, more study is required to define better the influence of age on the neuromuscular blockade produced by vecuronium.

Succinylcholine

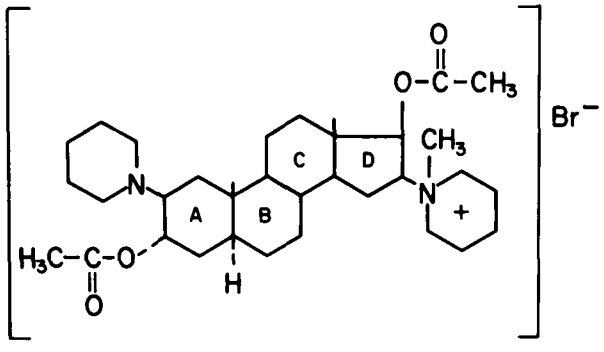
Previous administration of succinylcholine probably enhances the neuromuscular blockade from vecuronium.[9,41] As with pancuronium[42,43] and *d*-tubocurarine,[44,45] however, there is lack of agreement among investigators. D'Hollander et al[46] found that succinylcholine augmented both the magnitude and duration of a vecuronium-induced neuromuscular blockade. This augmentation occurred when vecuronium was given within 30 minutes of succinylcholine administration. Krieg et al[41] noted that vecuronium given after succinylcholine caused 19% greater depression of twitch tension than did vecuronium given without a prior dose of succinylcholine. Yet Fisher and Miller[47] reported that prior administration of succinylcholine did not alter a vecuronium-induced neuromuscular blockade. Clearly, the response to vecuronium is dependent on the time interval between its administration and that of succinylcholine.

Acid-Base Balance

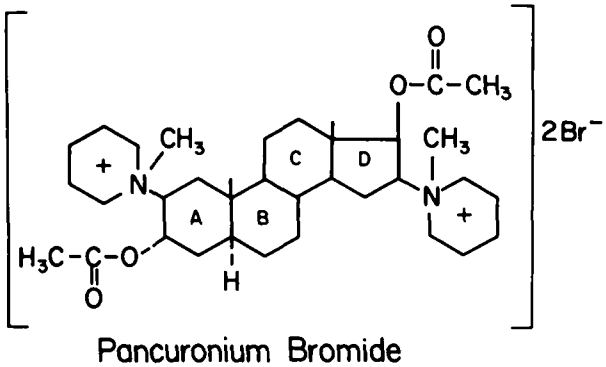
In cats, Funk et al[48] demonstrated that acidosis augmented and alkalosis lessened a vecuronium-induced neuromuscular blockade. In humans, Gencarelli et al[49] found that the timing of changes in end-tidal partial pressure of carbon dioxide (P_{CO_2}) was important as to its influence on vecuronium. During an end-tidal P_{CO_2} of 25, 41 or 56 mm Hg, neither the magnitude of nor recovery time from a vecuronium-induced neuromuscular blockade changed. 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 (Figure 4). Thus if respiratory acidosis occurs during vecuronium-induced neuromuscular blockade, an augmented and prolonged blockade may result.

Cardiovascular Effects

The two major cardiovascular effects from older nondepolarizing blockers are tachycardia (e.g., pancuronium and gallamine) and hypotension from histamine release (e.g., *d*-tubocurarine and metocurine). In contrast, vecuronium has few or no cardiovascular effects. For example, Booij et al[50] gave three times the ED_{90} of vecuronium i.v. to dogs and noted no change in heart rate, blood pressure



Vecuronium Bromide



Pancuronium Bromide

Figure 4. The relationship between acute changes in P_{CO_2} and subsequent changes in twitch tension in patients receiving vecuronium. Each point represents the data for one patient. (Reprinted with permission. From reference 49).

and cardiac output. Marshall et al[51] 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 were essentially free of cardiovascular effects.[27] Finally, vecuronium does not release histamine.[52]

Gregoretti et al[53] administered vecuronium 0.1 mg/kg i.v. to patients anesthetized with enflurane and halothane. The only cardiovascular change was a slight decrease in heart rate (from 76 to 63 b/min) during halothane anesthesia; however, the control heart rate was obtained before both vecuronium and halothane were administered. The authors 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[54] found no change in heart rate, arterial blood pressures or systolic time intervals from vecuronium 57 μg/kg i.v. given to patients also anesthetized with halothane. To test severely vecuronium's apparent lack of cardiovascular effects. Morris et al[55] gave 0.28 mg/kg (6 to 12 times the ED_{90}) of vecuronium i.v. 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%.[56] Also, Gencarelli et al[56] gave vecuronium 0.10–0.14 mg/kg as an intravenous bolus to three patients undergoing removal of a pheochromocytoma; there were small increases in plasma catecholamine concentrations in blood, but no change in any measured cardiovascular variables.

Antagonism

There have been no reports of difficulty in antagonizing a vecuronium-induced neuromuscular blockade with anticholinesterase drugs. Fahey et al[4] 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 Miller[57] continuously infused either pancuronium or vecuronium and noted no difference in the neostigmine dose required for antagonism. They concluded that vecuronium and pancuronium are effectively and equally (independent of their pharmacokinetics) antagonized by neostigmine. Baird et al[58] reported that edrophonium 0.5–1.0 mg/kg i.v. rapidly (i.e., 1–2 min) restored a vecuronium-depressed twitch to within 80% of control height, but that an additional 6–8 minutes were required for complete restoration of neuromuscular function, as judged by the train-of-four.

Special Clinical Situations

Cardiac Surgery and Cardiopulmonary Bypass

Because it has little or no cardiovascular effect, vecuronium may be an appropriate neuromuscular-blocking drug for cardiac surgery.[55] Still, one must question whether it is appropriate to rely on agents with relatively short durations of action for a procedure that requires several hours of paralysis. In other words, why not administer metocurine or pancuronium instead of vecuronium? The duration of action of vecuronium could be extended by giving very large doses. For example, Morris et al[55] administered 0.28 mg/kg and found the duration of action to be about 174 minutes.[4] Also, very large doses can be given with no cardiovascular effects.

The lack of cardiovascular effects associated with large doses of vecuronium can be a disadvantage with high-dose fentanyl anesthesia. Pancuronium is commonly used because 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.[59]

Hypothermia and cardiopulmonary bypass also can affect the amount of vecuronium required for neuromuscular blockade. Buzello et al[60] 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- and 5-fold 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 vecuronium.

Obstetrics

Baraka et al[61] gave vecuronium 0.05 mg/kg to patients undergoing cesarean section after they had recovered from an initial dose of succinylcholine. The mean duration of neuromuscular blockade was 19 minutes. Furthermore, Apgar scores did not differ for infants delivered before (N = 19) and after vecuronium administration (N = 19). Dailey et al[62] confirmed that vecuronium has 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[63] noted a ratio of 0.11 for vecuronium. Finally, plasma clearance of

vecuronium is more rapid than that of pancuronium in pregnant patients, probably because of cardiovascular and fluid shifts during pregnancy.[62] Although the increased clearance rate during pregnancy presumably results in a shorter neuromuscular blockade, this assumption has not been verified.

Renal Disease

Because vecuronium does not depend heavily on the kidney for its elimination, duration of neuromuscular blockade should not be prolonged in patients with renal failure. This conclusion has indeed been confirmed with large doses (0.28 mg/kg)[26] (Tables 2 and 3).

Table 3. Pharmacodynamics of Vecuronium (0.14 mg/kg) in Patients with and without Renal Function

Renal Function	Onset Time (min)	Duration (min)	Recovery Time[a] (min)
Normal	2.1	103	21
Absent	1.8	104	29

From reference 26.
[a]Defined as time from 25–75% recovery of twitch tension.

Liver Disease

Vecuronium has a rapid hepatic uptake and is significantly eliminated in the bile; thus one might predict that liver disease would prolong a vecuronium-induced neuromuscular blockade. After 0.2 mg/kg i.v. was given to patients with cirrhosis, elimination half-life increased from 58 to 84 minutes, and plasma clearance decreased 50%.[64] Also, the duration of neuromuscular blockade increased from 62 to 130 minutes.[64] Protein binding of vecuronium was not altered by the presence of cirrhosis.[65] Thus, the duration of neuromuscular blockade produced by vecuronium will be increased in patients with impaired hepatic function.

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Commentaries

Commentary 1

The most unique property of vecuronium that anesthesiologists should find attractive is its lack of cardiovascular effect. Vecuronium is the first nondepolarizing neuromuscular blocking drug introduced into clinical practice that has no cardiovascular effect within the entire clinical dose range. This fact has been amply demonstrated in many clinical studies. For this reason, vecuronium would seem to be especially indicated in patients with severe cardiac disorders, such as severe congestive failure, cardiogenic shock, etc. Another indication might be in conditions of severe hypovolemia where any vasodilator property might precipitate hypotension or shock. The drug is not ideal for all such situations, however. For example, many patients undergoing cardiac surgery are receiving large doses of β-adrenergic blocking drugs and/or calcium channel blockers. These individuals are commonly anesthetized with large doses of fentanyl, which causes bradycardia. In these situations where vecuronium is used as the neuromuscular blocking drug, narcotic-induced bradycardia is unopposed and may require treatment with an anticholinergic.

Another important area where vecuronium represents an advance with respect to currently available drugs is renal failure. It is unique among nondepolarizers in requiring primarily biliary rather than renal clearance.

In general, the intermediate duration of action of vecuronium (between those of succinylcholine and pancuronium) and its relatively rapid recovery pattern, will make it useful for shorter operations (e.g., two hours or less). Many anesthesiologists may find the somewhat faster onset of action (versus pancuronium, metocurine or d-tubocurarine) convenient for use to facilitate tracheal intubation.

Vecuronium will probably not "replace" any current drug. Both vecuronium and atracurium, the other intermediate-duration relaxant recently introduced, will add to the anesthesiologist's options for provision of surgical relaxation and find their own places in the practice of individual