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The Pharmacodynamics and Pharmacokinetics of Vecuronium in Patients Anesthetized with Isoflurane with Normal Renal Function or with Renal Failure

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The duration of action and the pharmacokinetics of vecuronium were compared in patients with and without renal function. Twenty patients were studied: 12 with renal failure who were to receive kidney transplants from cadaveric donors, and eight with normal renal function. After oral premedication with diazepam, 10 mg, anesthesia was induced with thiopental, 4 mg/kg iv, and maintained with the inhalation of 60% nitrous oxide and 0.9–1.1% isoflurane, end-tidal concentration, in 40% oxygen. The force of thumb adduction in response to supramaximal ulnar nerve stimulation was monitored and recorded. An intravenous bolus of vecuronium, 0.1 mg/kg, was administered after 15 min of a stable end-tidal isoflurane concentration, as measured by mass spectrometry. Venous blood was then sampled at frequent intervals for 4 h following the bolus. Vecuronium concentrations in plasma were quantified by a sensitive and specific gas chromatographic assay. Data were analyzed by nonlinear least squares regression and described by a two-compartment model. The duration of neuromuscular blockade was longer in patients with renal failure than in those with normal renal function. This increased duration may be related to both a decreased plasma clearance and a prolonged elimination half-life of vecuronium in the renal failure group. (Key words: Anesthetics, volatile: isoflurane. Kidney: failure. Neuromuscular Relaxants: vecuronium. Pharmacology: Pharmacodynamics; pharmacokinetics.)

THE INFLUENCE OF RENAL FAILURE on the pharmacodynamics and pharmacokinetics of vecuronium has not been clearly established. Initially, Fahey *et al.* demonstrated that neither the duration of neuromuscular blockade nor the pharmacokinetics of vecuronium differed according to the patient's renal status.[1] However, Bencini *et al.* found that the absence of renal function did decrease the plasma clearance of vecuronium.[2] Subsequently, these investigators concluded that the duration of action and the recovery rate, as well as the pharmacokinetics of vecuronium, were only mildly altered in patients with renal failure.[3] Meistelman *et al.* demonstrated that renal dysfunction prolonged recovery following vecuronium-induced blockade, but did not affect vecuronium plasma clearance or duration of action.[4] In the present study, we address these differences and attempt to enhance our understanding of the neuromuscular blocking properties of vecuronium in patients with renal failure. Accordingly, we compared the duration of action and the pharmacokinetics of vecuronium in patients with and without renal failure.

Materials and Methods

With approval from our Committee on Human Research and written, informed consent, we studied 12 patients with renal failure and eight with normal renal function. Those with normal renal function were ASA physical status I or II patients scheduled for various types of elective surgery. Renal failure patients were scheduled to receive cadaver kidney transplants and had been dialyzed within 12 h prior to surgery. They had a mean serum creatinine concentration of 12.3 ± 4.4 mg/dl.

Approximately 1 h after premedication with oral diazepam, 10 mg, anesthesia was induced in all patients with thiopental, 4 mg/kg iv, and by the inhalation of 60% nitrous oxide and increasing concentrations of isoflurane in oxygen. The trachea was intubated without the use of neuromuscular blocking drugs. Anesthesia was maintained with nitrous oxide 60%, oxygen 40%, and isoflurane, 0.9–1.1% end-tidal concentration, as measured by mass spectrometry. Ventilation was controlled to maintain the end-tidal P_{CO_2} between 35 and 40 mmHg. Esophageal temperature was maintained between 35 and 36.5° C by surface warming. The adductor pollicis twitch was elicited by supramaximal ulnar nerve stimulation delivered by a Grass S44 stimulator (0.15 Hz at 0.15 msec duration) through 27-gauge needle electrodes at the wrist. The resultant force of thumb adduction was quantified by a Grass FT10 transducer and recorded on a polygraph.

An iv bolus of vecuronium, 0.1 mg/kg, was administered following 15 min of stable end-tidal isoflurane

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TABLE 1. Onset, Beginning of Spontaneous Recovery, and Clinical Duration of Action for Vecuronium in Patients With or Without Renal Failure*

	n	Normal Renal Function	n‡	Absent Renal Function
Onset time	7	1.8 ± 0.6	12	1.9 ± 0.8
Beginning of spontaneous recovery	7	40.4 ± 24.9	9	60.6 ± 20.4
Clinical duration of action	7	54.1 ± 25.2	7	98.6 ± 37.7†

All times are in minutes.
* Values represent mean ± SD.
† Significant difference, $P < 0.05$.
‡ The n value in the patients without renal function decreased from 12 to 9 because three patients had not begun spontaneous recovery at the times noted in the manuscript. In addition, two other patients, who did show spontaneous recovery, did not recovery to 25%, and only seven patients could be used for the clinical duration of action.

concentrations. Venous blood (5 ml/sample) was drawn into a heparinized syringe at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min after vecuronium administration. The blood samples were cooled to 0–4° C and centrifuged. The resultant plasma was acidified with 0.8 M sodium dihydrogenphosphate to a *p*H of 4.7 ± 0.1. All samples were stored at −30° C until analysis.

Plasma vecuronium and its 3-desacetylvecuronium metabolite levels were measured by capillary gas chromatography using a nitrogen sensitive detector. This assay is linear over the range of 2–5000 ng vecuronium/ml and 4–5000 ng 3-desacetylvecuronium/ml with a precision (coefficient of variation) of 2–15%.‡‡

The onset time (time from injection to maximum effect), the time from injection to the beginning of spontaneous recovery of twitch tension, and the clinical duration of action (time from injection to 25% recovery of control twitch tension) were measured. Control twitch tension was defined by the tension measurement taken prior to the administration of vecuronium.

The vecuronium plasma concentration *versus* time data were analyzed by nonlinear least squares regression, and pharmacokinetic models of two and three compartments were derived using the BMDP statistical program.[5] To compare models and assign the best fit, we applied the criteria of Boxenbaum *et al.*,[6] and determined that the data were best described by a two-compartment open pharmacokinetic model. The following parameters were determined using standard formulas: distribution half-life ($t_{1/2}\alpha$), elimination half-life ($t_{1/2}\beta$), central compartment volume (V_1), volume of distribution at steady state (Vd_{ss}), and clearance (Cl).[7]

The twitch tension measurements, as well as the pharmacokinetic values, obtained in the presence and absence of renal function, were compared using the Mann-Whitney rank test.[8] Differences were considered statistically significant when the *P* value was less than 0.05.

Results

Onset time and the time from injection to the beginning of spontaneous recovery did not differ significantly between patient groups (table 1). However, the clinical duration of neuromuscular blockade (mean ± S.D., minutes) was longer in patients with renal failure 98.6 ± 37.7 *versus* 54.1 ± 25.5 in those with normal renal function. Three patients in the renal failure group failed to achieve spontaneous recovery at 123.6, 135.9, and 161.2 min, respectively (table 1). In these patients, neuromuscular function did recover after isoflurane was discontinued and blockade was reversed with neostigmine. The results from these patients were not included in the calculation of the spontaneous recovery time or of the clinical duration of neuromuscular blockade. Two additional patients in this group, who did demonstrate spontaneous recovery, did not achieve recovery to 25% of control twitch tension. In one of these patients, additional muscle relaxant (d-tubocurarine) had been administered at 98 min after bolus injection of vecuronium at the request of the surgeon. Twitch height in this patient at that time was 9% of control. In the second patient, neuromuscular blockade had to be reversed with neostigmine, at 200 min (twitch height was 20% of control), at the conclusion of the surgery.

Figures 1 and 2 illustrate the vecuronium plasma concentration *versus* time data obtained for each patient in each group. The data from all of the renal failure patients were included in this analysis. Data from only seven of the eight patients having normal renal function were included because one patient was discovered, retrospectively, to have a significant past medical history including both renal disease (chronic pylonephritis) and hepatic disease (hepatitis A). The pharmacokinetic parameters derived from these curves appear in table 2. In addition to a significantly lower clearance rate (Cl), patients without renal function demonstrated a significantly longer elimination half-life ($t_{1/2}\beta$) for vecuronium. However, the volume of distribution at steady state (Vd_{ss}) and the initial volume of distribution (V_1) did not differ significantly between groups.

The times to spontaneous recovery and the durations of action, as well as the pharmacokinetic parameters,

‡‡ Furuta T, Canfell PC, Castagnoli KP, Sharma ML, Miller RD: Quantitation of pancuronium, 3-desacetylpancuronium, vecuronium, 3-desacetylvecuronium, pipecuronium and 3-deacetylpipecuronium in biological fluids by capillary gas chromatography using nitrogen-sensitive detection. Unpublished observations, 1987.

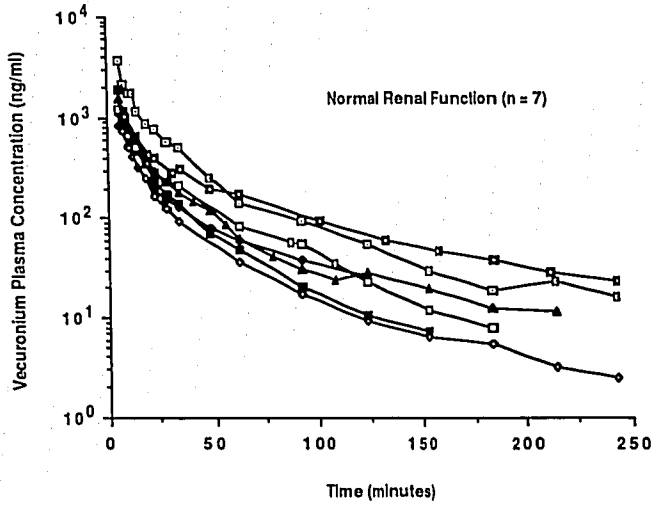

FIG. 1. Plasma vecuronium concentration *versus* time relationship for each patient with normal renal function.

displayed considerable variability within each group. However, in the control group, patients with longer durations of action tended to have lower clearance values. The plot of duration *versus* clearance (fig. 3) demonstrates that there is a high correlation between the two values, with a coefficient of determination (r^2) of 86.9 and a standard error of the estimate of 11.5.[9] In contrast, it is apparent that this correlation is poor in patients undergoing renal transplantation (fig. 3), with a coefficient of determination of 25.8 and a standard error of the estimate of 35.7.[9]

Discussion

Our results indicate that the clinical duration of action of vecuronium is significantly prolonged in patients with renal failure. Furthermore, this prolongation is related to a decreased clearance of vecuronium from the plasma in renal failure patients as compared to patients who have normal renal function. These results are not surprising, recognizing that between 20 and 30% of an injected dose of vecuronium is dependent on the kidney for its elimination.[2]

TABLE 2. Vecuronium Pharmacokinetics: A Comparison Between Patients With or Without Renal Failure

	Normal Renal Function n = 7	Absent Renal Function n = 12
$t_{1/2\alpha}$ (min)	7.53 ± 2.26	11.30 ± 4.98*
$t_{1/2\beta}$ (min)	52.57 ± 17.76	83.10 ± 28.79*
V_1 ($l \cdot kg^{-1}$)	0.093 ± 0.027	0.109 ± 0.036
Vd_{ss} ($l \cdot kg^{-1}$)	0.199 ± 0.069	0.241 ± 0.071
Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	5.29 ± 2.17	3.08 ± 0.83*

Values represent mean ± SD.
* Significant difference, $P < 0.05$.

In agreement with Bencini *et al.*,[2] we found a slower plasma clearance of vecuronium in patients who had no renal function *versus* those with normal function. In addition, we have shown, as did Bencini *et al.*,[2,3] Fahey *et al.*,[1] and Meistelman *et al.*,[4] that the steady-state volume of distribution for vecuronium is similar in the presence and absence of renal failure. Consequently, the increased duration of action and prolonged recovery index[4] observed during renal failure are not likely to be due to differences in drug distribution volumes. We found, as did the previous investigators,[1-4] that the volume of distribution of vecuronium was in excess of the blood, plasma, and extracellular fluid volumes, indicating that there may be extensive tissue localization of vecuronium, possibly in the liver. The biliary concen-

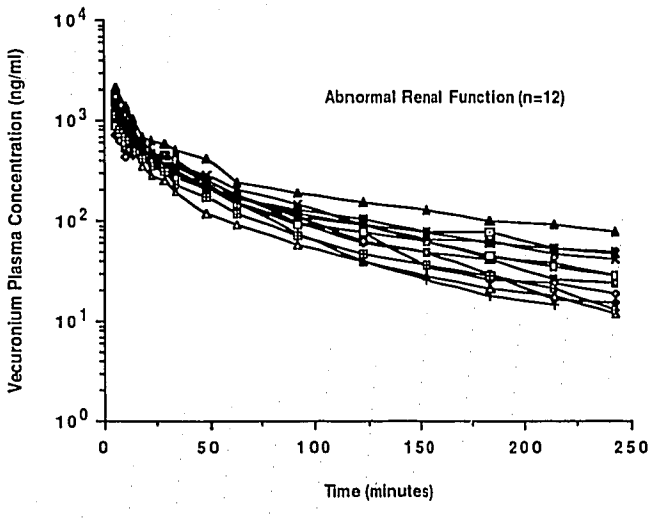

FIG. 2. Plasma vecuronium concentration *versus* time relationship for each patient with abnormal renal function.

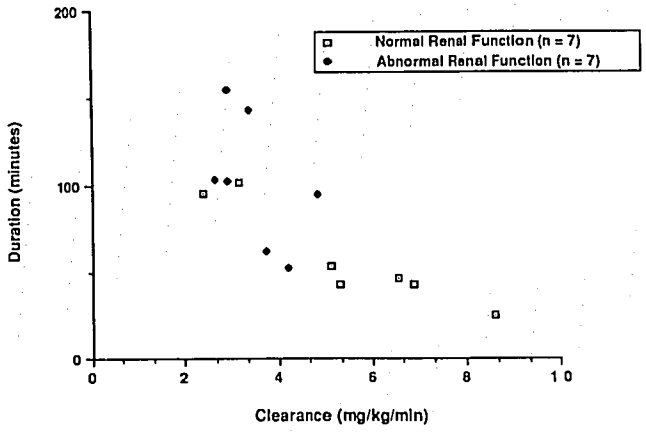

FIG. 3. The duration of action as a function of the plasma clearance of vecuronium is shown in patients with and without renal failure. The correlation was good ($r^2 = 86.9$) in patients with normal renal function ($y = 120 - 12.5x$), but was poor ($r^2 = 25.8$) in patients with abnormal renal function ($y = 180 - 23.9x$).

tration of vecuronium was measured by Bencini *et al.*[2] *via* a T-tube drain over a 24-h period following administration of an 0.15 mg/kg iv dose. Very high concentrations of the drug, *e.g.*, 60 μg/ml at 20 min after injection, were detected, suggesting that approximately 40–80% of a vecuronium dose may be taken up by the liver in the first 30 min after injection.[2] These investigators also found high concentrations of vecuronium in biopsied human liver specimens analyzed at 30 min after an iv injection of a similar dose of vecuronium.[2]

We found, as did Bencini *et al.*,[3] that vecuronium disappears more slowly from the plasma of patients with renal failure. This results in vecuronium plasma concentrations that are higher in renal failure patients at any time following vecuronium administration. As can be seen in figure 1, six of the eight patients who had normal renal function had a vecuronium plasma concentration of less than 100 ng/ml at 60 min. In contrast, 11 of the 12 patients who had absent renal function had a vecuronium plasma concentration, at 60 min, of greater than 100 ng/ml. The effective plasma concentration at 50% recovery of the control twitch height, for a vecuronium-induced neuromuscular blockade, has been shown to be 110 ng/ml.[10]

A previous study by Fahey *et al.* demonstrated that there were no significant differences between patients with and without renal function in onset time, duration (time from injection to 90% recovery of control twitch tension), or recovery time following administration of vecuronium.[1] Although we used a similar method to quantify and record the adductor pollicis tension in response to single-twitch stimulation, the duration of stimulation applied by their study was longer (0.15 Hz at 0.2 msec) than ours (0.15 Hz at 0.15 msec). Ali and Saverese[11] suggest that the period of stimulation applied in the Fahey study is at the upper limit of normal, close to the threshold at which a stimulus of longer duration may cause repetitive firing of the nerve. However, we feel that it is highly unlikely that this would account for pharmacodynamic difference between the two studies. One significant difference between our study and others is the use of isoflurane as the maintenance anesthetic rather than halothane (Fahey *et al.*[1] and Bencini *et al.*[2,3]). Meistelman *et al.*, who found a comparable duration of action but longer recovery index than did we in patients with renal failure, maintained anesthesia with nitrous oxide and fentanyl.[4] In fact, clinical studies of the influence of renal failure on the action of muscle relaxants have not used isoflurane as their primary anesthetic. We can thus speculate that one explanation for the difference between our results and the others is that isoflurane augmented the increased plasma concentration of vecuronium to prolong neuromuscular blockade in patients with renal failure. To be certain of this possibility, we would need to repeat the present study using another anesthetic to maintain anesthesia during neuromuscular blockade from the same dose of vecuronium (0.1 mg/kg), or clinically to administer a lower dose of vecuronium during isoflurane anesthesia.

Differences in assay methods may also help to account for the variation among studies in results. There are several different analytical techniques of variable specificities and sensitivities used in the quantitation of vecuronium in the plasma. Bencini *et al.* used a combined fluorimetric-thin layer chromatographic assay.[2,3] The total amount of vecuronium and metabolites in the plasma were first measured by fluorimetry, and the sample was then subjected to thin layer chromatography to distinguish between vecuronium and any deacetylated metabolites. The coefficient of variation of the fluorimetric technique was 3–10% in the 5–100 ng/ml range, and that of the thin layer chromatography technique was ±10%, with a detection limit of 150 ng of vecuronium. Meistelman *et al.* utilized only the fluorimetric assay, which did not separate vecuronium from its metabolites.[4] Fahey *et al.* assayed for vecuronium by using high performance liquid chromatography.[1] The sensitivity of this assay was only 50 ng/ml of serum. All of these techniques are insensitive to the low nanogram concentrations of vecuronium occurring at the terminal portion of the concentration *versus* time curve, and, therefore, may not give accurate information about the elimination half-life for vecuronium. In addition, the information that is derived using the fluorimetric assay may overestimate the $t_{1/2}\beta$ due to the inability to separate vecuronium from its metabolites. The capillary gas chromatographic assay developed in our laboratory allowed simultaneous determinations of vecuronium to as low as 2 ng/ml of plasma, and its deacetylated analogs. Consequently, our concentration *versus* time curve was only derived from the vecuronium concentration in plasma, without contribution from metabolites. Our method thus yields the most accurate estimate of the terminal phase of elimination. A comparison of our $t_{1/2}\beta$ values with those of Fahey *et al.*[1] and Bencini *et al.*[3] indicated that we demonstrated a shorter elimination half-life in both the patients with normal renal function (53 *vs.* 80 *vs.* 117 min.), as well as those with renal failure (83 *vs.* 97 *vs.* 149 min.).

The pharmacokinetic model developed was similar to that of Fahey *et al.*[1] and Meistelman *et al.*,[4] a biexponential equation and a two-compartment model describing the plasma concentration decay curve for vecuronium. Bencini *et al.* selected a triexponential function to describe the kinetics.[2,3] If our sampling time had been greater than 240 min, we might also have developed a three-compartment model, as did Cronnelly *et al.*,[12] using a highly sensitive mass spectrometric assay for ve-

curonium having a lower limit of detection of 2 ng/ml and sampling for 480 min. As can be seen in figure 1, at 240 min, all renal failure patients had plasma vecuronium concentrations >10 ng/ml. Because significant amounts of vecuronium were present in the plasma of renal failure patients at this sampling time, it is possible that a longer sampling time would have fitted the vecuronium plasma concentration curve to a three-compartment model.

Miller *et al.*[13] have found that a newly transplanted kidney is capable of excreting d-tubocurarine. In our study, we did not determine the extent to which vecuronium may have been excreted by the transplanted kidney after initiation of renal perfusion and probable improvement of renal function. However, if we assume that the maximum amount of vecuronium was excreted in the urine after unclamping of the renal artery, we still demonstrated a decreased plasma clearance and increased elimination half-life in these patients. We, therefore, may have actually overestimated the plasma clearance of vecuronium in patients with renal failure, and can conclude that its elimination is related to renal mechanisms.

The present investigation demonstrated a considerable amount of variability in the pharmacodynamic and pharmacokinetic parameters within each group. However, patients with normal renal function did show a strong correlation between the duration of neuromuscular blockade and clearance rate (fig. 3). The large variability in the renal failure group did not correlate with any one pharmacokinetic parameter. Other investigators have seen great variability in the determination of the pharmacokinetics and pharmacodynamics of other neuromuscular relaxants (d-tubocurarine[13] and pancuronium[14]) in patients with renal failure. Conceivably, renal disease may change the pharmacokinetics of a drug in various ways. It may either be direct through an alteration in plasma clearance, hypoalbuminemia, changes in protein molecular structure, and competition for drug binding sites with other endogenous substances that may accumulate in renal failure; or indirect due to potentially adverse interactions with associated diseases such as diabetes and anemia.[15]

In conclusion, vecuronium produced a longer neuromuscular blockade in patients with renal failure during an isoflurane anesthetic. We have also shown that this increased duration of neuromuscular blockade does have a pharmacokinetic correlation, although the significant variability within the group is probably explained by a number of different and interacting factors. The neuromuscular blockade produced in these patients, albeit longer, was never irreversible. However, if vecuronium is chosen as the neuromuscular blocking agent for patients with or without renal function, during an isoflurane anesthetic, a smaller dose than 0.1 mg/kg should be administered.

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