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Pharmacokinetics of Rocuronium Bromide (ORG 9426) in Patients with Normal Renal Function or Patients Undergoing Cadaver Renal Transplantation

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To determine the effect of end-stage renal disease on the pharmacokinetics of rocuronium bromide (ORG 9426), a new nondepolarizing monoquaternary steroidal neuromuscular blocking drug, the authors administered 600 μg/kg rocuronium (2 × ED_{95}) intravenously to ten patients undergoing cadaver renal transplantation and ten healthy patients undergoing elective minor surgery (controls). All patients were anesthetized with nitrous oxide (50–70% in oxygen) and isoflurane (end-tidal concentrations of 1.2 ± 0.5% and 0.8 ± 0.2%, mean ± SD, for control and transplant groups, respectively). Plasma concentrations of rocuronium were determined by capillary gas chromatography. A population-based pharmacokinetic analysis (NONMEM) was used to determine typical values, standard errors, and interindividual variability for the pharmacokinetic parameters and to determine whether these values differed between control and renal transplant patients. Total plasma clearance (2.89 ± 0.25 ml · kg^{-1} · min^{-1}, mean ± SE) and volume of the central compartment (76.9 ± 10.6 ml/kg) did not differ between control and renal transplant patients, whereas volume of distribution at steady state was greater in renal transplant patients (264 ± 19 ml/kg) than in control patients (207 ± 14 ml/kg). This resulted in a longer elimination half life in renal transplant patients (97.2 ± 17.3 min) compared to controls (70.9 ± 4.7 min). The authors conclude that renal failure and renal transplantation alter the distribution but not the clearance of rocuronium. (Key words: Kidney failure: muscle relaxants. Neuromuscular relaxants: rocuronium bromide (ORG 9426). Pharmacokinetics: rocuronium bromide (ORG 9426). Transplantation: kidney.)

IN THE SEARCH for a nondepolarizing neuromuscular blocking drug with a rapid onset of action, rocuronium bromide (ORG 9426) was developed.[1] In both animals[1,2] and humans,[3–5] it has a rapid onset and an intermediate duration of action. In humans, it produces good to excellent tracheal intubating conditions in 60–90 s after administration,[6] is five to six times less potent than vecuronium,[4,5] and has little or no cardiovascular effect.[4,5] The focus of the current study was to determine the influence of renal failure and renal transplantation on the pharmacokinetics of rocuronium in humans. Accordingly, we compared the pharmacokinetics of rocuronium in patients with normal renal function with those in patients with end-stage renal disease undergoing cadaver renal transplantation.

Materials and Methods

With approval from our local Committee on Human Research and informed written consent, we studied 20 patients. Ten patients had no historic or laboratory evidence of renal or hepatic disease (23–65 yr of age, ASA physical status 1 or 2) and underwent elective surgery not involving the liver or kidney. The remaining ten patients had end-stage renal disease (21–45 yr of age, ASA physical status 3) and were undergoing cadaver renal transplant. Exclusion criteria included child-bearing potential; known neuromuscular disorders; obesity (defined as weight exceeding 130% of ideal body weight); or known allergy to benzyl alcohol, opioids, or other medications used during anesthesia. Patients chronically receiving antihistamines, anticonvulsants, aminoglycoside, or polypeptide antibiotics or having clinically significant renal, cardiac, or hepatic disease also were excluded from the study. After administration of midazolam 0.02–0.08 mg/kg intravenously, anesthesia was induced with thiopental 1–4 mg/kg intravenously, followed by inhalation of nitrous oxide 50–70% in oxygen, with up to 4% isoflurane (inspired concentration). The trachea was intubated without administration of a muscle relaxant. Anesthesia was maintained with 50–70% nitrous oxide and isoflurane (end-tidal concentrations of 1.2 ± 0.5 and 0.8 ± 0.2%, mean ± SD, for control and transplant groups, respectively) monitored by mass spectrometry. Ventilation was controlled to keep end-tidal P_{CO_2} between 32 and 42 mm Hg; esophageal temperature was maintained at 35–37° C.

The ulnar nerve was stimulated supramaximally at the wrist using train-of-four stimuli at 2 Hz applied every 12

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s. Stimuli of 0.2-ms duration were delivered *via* needle electrodes from an S88 nerve stimulator (Grass Instrument Co., Quincy, MA); twitch tension of the adductor pollicis was measured with a Statham UTC3 force transducer (Gould, Inc., Cleveland) and recorded on a Gould 220 polygraph. A resting tension of 150–300 g was applied to the thumb. After anesthetic conditions and twitch tensions had been stable for at least 15 min, rocuronium 600 μg/kg (2 × ED_{95} reported by Foldes *et al.*[4]), was rapidly injected intravenously. Neuromuscular blockade was recorded from the time of administration of rocuronium until either 1) the end of surgery, at which time residual neuromuscular blockade was antagonized with neostigmine and glycopyrrolate (0.04–0.07 mg/kg and 0.008–0.014 mg/kg, respectively) if the ratio of the fourth component of the train-of-four to the first was less than 75%, or 2) additional muscle relaxation was required, at which time atracurium, which does not interfere with measurement of rocuronium, was administered. We calculated the times from administration of rocuronium until complete ablation of the first twitch (onset), until the first twitch recovered to 25% (clinical duration) and 90% of control (relaxation time), and the time for the twitch to recover from 25% to 75% of control (recovery time).

Venous blood samples (4 ml each) were drawn from the contralateral arm before and at 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 300, and 360 min after administration of rocuronium. In the first seven control studies, samples were obtained for 240 min only; in addition, in one subject with renal failure, interfering peaks prevented determination of rocuronium concentrations beyond 240 min. Blood samples were anticoagulated with heparin, iced, and centrifuged within 1 h of collection. Plasma was mixed with an equivalent volume of 0.8 M sodium dihydrogen phosphate and was stored at −30° C until analysis. Plasma concentrations of rocuronium were determined after single methylene chloride ion-pair extraction, derivatization with N-methyl-N-(t-butyldimethylsilyl) trifluoroacetamide, and injection into a gas chromatograph equipped with a nitrogen–phosphorus detector.[7] This method is sensitive to 10 ng/ml with coefficient of variation of < 10% at 20 ng/ml. Chromatograms were also examined for the presence and magnitude of peaks consistent with ORG 9943 (17-desacetylrocuronium), a putative metabolite of rocuronium.

Pharmacokinetic values were determined using the NONMEM program.‡‡ In contrast to the traditional approach, in which pharmacokinetic parameters are estimated separately for each individual, NONMEM analyzes data for populations and provides estimates for "typical values" of the pharmacokinetic parameters, standard errors (precision) of these estimates, and interindividual variability within the population. Two- and three-compartment pharmacokinetic models were fit to the rocuronium plasma concentration data. These models were parameterized in terms of volume of the central compartment (V_1), volume of the second and, if appropriate, third compartment (V_2, V_3), clearance (Cl), rapid distributional clearance (Cl_{rapid}, the intracompartmental rate constant for drug movement from the central to second compartment, equal to $V_1 \cdot k_{12}$), and, if appropriate, slow distributional clearance (Cl_{slow}, the intracompartmental rate constant for drug movement from the central to third compartment, equal to $V_1 \cdot k_{13}$). Volume of distribution at steady state (V_{SS}) was calculated as the sum of V_1, V_2, and V_3. For the two-compartment model, distribution and elimination half-lives were calculated using standard formulas.[8] For the three-compartment model, rapid and slow distribution half lives ($t_{1/2}\pi$ and $t_{1/2}\alpha$, respectively) and elimination half-life ($t_{1/2}\beta$)[8] were determined iteratively.§§

Interindividual variability was modeled by assuming that each individual's pharmacokinetic parameters can be expressed as the sum of the typical value for the population and a factor for that individual. Because interindividual variability tends to assume a log-normal (*i.e.*, skewed) distribution, interindividual variability for clearance was modeled as:

$$\ln(Cl_i) = \ln(Cl) + \eta_i$$

where Cl_i is the estimate for clearance for the ith individual; Cl is the typical value for the population; and η_i is a random variable with mean 0.0. Equation 1 can also be written as:

$$Cl_i = Cl \cdot \exp(\eta_i)$$

Interindividual variability for V_1, V_2, and V_3 were modeled in a similar manner except that interindividual variability was assumed to be the same for V_2 and V_3.

The effect of renal function was determined by comparing pharmacokinetic models in which "typical values" for parameters (*i.e.*, Cl) were either the same or different for subjects with normal renal function and subjects undergoing renal transplantation. These models were compared by their effects on the objective function (NONMEM's equivalent of the residual sum of squares for traditional nonlinear regression analysis), the residual differences between observed and predicted plasma concentrations, and interindividual variability. Renal function was entered into the model as a dichotomous variable,

‡‡ Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, University of California, 1979.

§§ Microsoft Excel Solver User's Guide, Version 3.0a. Redmond, Microsoft Corporation, 1991.

TABLE 1. Demographic Data for All Patients

	Normal Renal Function	Renal Transplantation
n	10	10
Age (yr)	44 ± 15 (23–65)	36 ± 9 (21–45)
Weight (kg)	78 ± 12 (66–107)	69 ± 17 (45–98)
Gender (F/M)	3/7	3/7

Values for age and weight are mean ± SD; ranges are shown in parentheses.

i.e., absent or present. The influence of renal function on Cl, V_1, V_2, and V_3 (the effect on V_2 and V_3 were assumed to be identical) were tested separately and in combination. The influence of renal function on each of these pharmacokinetic parameters was included in the model if the improvement of the objective function attained statistical significance (using a conservative criteria of $P < 0.005$; *i.e.*, the larger model improved the objective function by 7.6).

Additional issues addressed in the analysis included:

1. Is the addition of a third pharmacokinetic compartment justified?
2. Are estimates of the pharmacokinetic parameters improved by normalizing them for weight?
3. Are estimates of the pharmacokinetic parameters improved by normalizing them for ideal body weight?
4. Are estimates of the pharmacokinetic parameters influenced by the duration of sampling (*i.e.*, for subjects in whom data were obtained for 360 min, were pharmacokinetic estimates that were based on the initial 240 min of plasma concentration data different from those using all plasma concentration data)?
5. Does perfusion of the newly transplanted kidney alter the pharmacokinetics of rocuronium? This was tested by permitting a step change in Cl, V_1, or V_2, V_3 at the time that the kidney was revascularized.

Urine was collected for 24 h from three patients with normal renal function and from nine undergoing renal transplantation. Rocuronium concentrations were determined using the same assay as for plasma to determine the percentage of rocuronium eliminated *via* the kidney.

Results

There were no differences between groups with respect to age, body weight, or gender (table 1). Transplanted kidneys were revascularized at 181 ± 104 min (range 58–424 min) following administration of rocuronium. "Average" plasma concentrations (determined using a smoother, Supersmoother¶¶) for the first 30 min after rocuronium administration were similar for the two groups; thereafter, plasma concentrations were lower in control patients (figs. 1 and 2).

Examination of the residuals (*i.e.*, differences between the observed and predicted plasma concentrations) suggested that the two-compartment model was not adequate to describe the data. Use of a three-compartment model markedly improved the objective function ($P < 0.005$); in addition, examination of the residuals no longer suggested model-misspecification. Estimates of Cl, V_1, and V_{ss} for control patients differed less than 10% when the limited (≤ 240 min) and complete data sets were used; similar results were obtained for renal transplant patients.

Estimates of the pharmacokinetic parameters showed

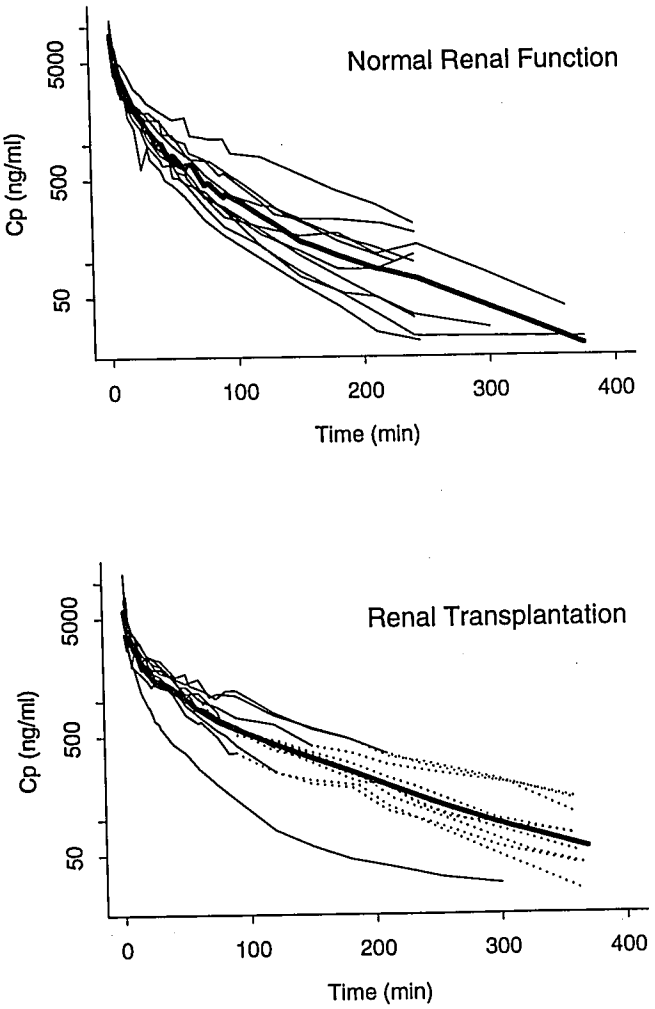

FIG. 1. Plasma concentration (Cp) *versus* time data for individual patients with normal renal function (*top*) or patients undergoing renal transplantation (*bottom*) are shown. For subjects undergoing renal transplantation, the time at which the kidney is revascularized is indicated by a change from a solid to a dashed line. Lightface lines connect values for individual patients; the boldface line is the "average" plasma concentration determined using a smoother, supersmoother (see text).

¶¶ Modern Regression Methods. S-Plus User's Manual, Version 3.0. Seattle, Statistical Sciences, Inc., 1991, pp 1–46.

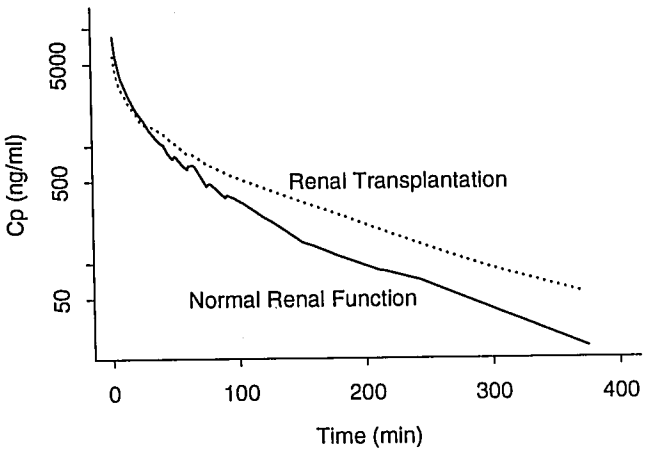

FIG. 2. "Average" plasma concentration (Cp) *versus* time data for patients with normal renal function (*solid line*) or patients undergoing renal transplantation (*dashed line*) are shown. "Average" values were determined using a smoother, supersmoother (see text).

similar or smaller variability (*i.e.*, the same or a smaller coefficient of variation) and a similar or improved objective function when normalized for body weight compared to those not normalized for body weight; a further improvement was obtained by normalizing for ideal body weight. For example, the objective function was 7.8 smaller with weight-normalized compared to nonnormalized values; normalizing for ideal body weight reduced the objective function an additional 16.7. Similar improvements existed for renal transplant patients. For the remaining pharmacokinetic analyses, all parameters were normalized for body weight.

Permitting renal function to influence V_1, and V_2, V_3 improved the objective function; the greater improvement of the objective function occurred when renal function influenced V_2 and V_3 (table 2). Permitting renal function to influence combinations of Cl, V_1, and V_2, V_3 did not improve the objective function further. Thus, the "optimal" model for the influence of renal function on the pharmacokinetics of rocuronium permitted V_2 and V_3 (and consequently, the derived parameters, V_{SS}, $t_{1/2}\pi$, $t_{1/2}\alpha$, and $t_{1/2}\beta$) to differ between control and renal transplant patients; V_1, Cl, Cl_{rapid}, and Cl_{slow} were identical for control and renal transplant patients (tables 3 and 4).

To evaluate whether perfusion of the newly transplanted kidney altered the pharmacokinetics of rocuronium, we permitted step changes in Cl, V_1, and V_2, V_3 at the time of renal revascularization. None of these step changes attained statistical significance.

Urinary excretion of rocuronium was 1%, 11%, and 22% in three patients with normal renal function and varied from 0–5% in nine patients undergoing renal transplantation. Because of the small sample size for subjects with normal renal function, these values were not compared statistically.

Rocuronium had a rapid onset of action, resulting in 100% neuromuscular blockade in < 90 s in all but two patients (both with normal renal function) in whom 100% blockade occurred at 94 and 125 s, respectively (table 5). Because of differences between groups in end-tidal anesthetic concentrations and because of the limited data regarding recovery in renal transplant patients (25–75% and 90% recovery times could be obtained in only four and five patients, respectively), we did not compare neuromuscular effects between groups.

Discussion

Our results show that the clearance and central compartment volume of rocuronium are similar in patients with normal renal function and those undergoing renal transplantation. However, V_2 and V_3 are greater in patients undergoing renal transplantation, resulting in a larger V_{SS} and a longer elimination half-life. In addition, this study confirms that a $2 \times ED_{95}$ dose of rocuronium has a rapid onset.

We initially collected blood samples for 240 min, expecting plasma concentrations of rocuronium to decrease below the detection limit of the assay at that time. However, because in initial studies plasma rocuronium concentrations at 240 min exceeded the limit of detection of the assay, we sampled for 360 min in subsequent studies. Because samples were obtained for only 240 min in the majority of patients with normal renal function, we performed our analyses twice, once using all of the data, and a second time using only concentrations from the first 240 min. Because the differences in the estimates for the

TABLE 2. Decrease in the Objective Function when "Typical Values" for Clearance, V_1, or V_2, V_3 Are Permitted to Differ Between Subjects with Normal Renal Function and Subjects Undergoing Renal Transplantation

Parameters Allowed to Vary Between Groups	Decrease in Objective Function
No additional parameters	0
One additional parameter	
Cl	0.4
V_1	12.1*
V_2, V_3	24.5*
Two additional parameters	
Cl, V_1	18.0
Cl, V_2, V_3	24.9
V_1, V_2, V_3	31.3
Three additional parameters	
Cl, V_1, V_2, V_3	32.0

The influence of renal function on V_2 and V_3 was assumed to be identical (*i.e.*, the same additional parameter was used for both). See text for definitions of variables.

* Different from model containing fewer additional parameters ($P < 0.005$).

TABLE 3. Values for the Pharmacokinetic Parameters Obtained Using the Optimal Model

	Typical Value	Standard Error	Interindividual Variability*
Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	2.89	0.25	0.74–1.36
Cl_{rapid} ($ml \cdot kg^{-1} \cdot min^{-1}$)	8.79	1.05	Not estimated; see text
Cl_{slow} ($ml \cdot kg^{-1} \cdot min^{-1}$)	1.51	0.16	Not estimated; see text
V_1 ($ml \cdot kg^{-1}$)	76.9	10.6	0.48–2.07
V_2 ($ml \cdot kg^{-1}$)			
Normal renal function	50.3	5.3	0.68–1.44
Renal transplant	72.4	9.4	0.68–1.44
V_3 ($ml \cdot kg^{-1}$)			
Normal renal function	79.9	7.9	0.68–1.44
Renal transplant	115.0	9.5	0.68–1.44

See text for definitions of variables.
* Because interindividual variability is estimated using an exponential (see text), variability is not symmetric. Reported values are the range from one standard deviation below to one standard deviation above the typical value and are expressed as a fraction of the typical value.

pharmacokinetic parameters using the complete and limited data sets were small (< 10%), we report the pharmacokinetic parameters obtained using the complete data set.

If the newly transplanted kidney excreted significant amounts of rocuronium, one assumption that underlies our pharmacokinetic modeling, *i.e.* that clearance remains constant, would be invalid. However, our finding that urinary excretion of rocuronium was minimal (subjects undergoing renal transplantation excreted 1% or less of the administered dose, with the exception of one subject, who excreted 5% of the dose in the urine) suggests that the newly transplanted kidney eliminates rocuronium minimally. In addition, figure 1 suggests that revascularization of the transplanted kidney is not associated with a change in the slope of the plasma concentration *versus* time curve, and we were unable to demonstrate that perfusion of the transplanted kidney is associated with a step change in any of the pharmacokinetic parameters. This lack of effect of renal failure and renal transplantation on the clearance of rocuronium is consistent with the finding in cats that rocuronium is eliminated principally by hepatobiliary mechanisms: only 9% of an injected dose of rocuronium is excreted in the urine in 360 min, compared with 76% in the liver and bile over the same time period.[2]

Our finding that the clearance of rocuronium was not altered in patients undergoing renal transplantation contrasts the finding that vecuronium's clearance is decreased in these patients. For example, Lynam *et al.*[9] reported that vecuronium's clearance was decreased 42% in patients undergoing renal transplantation compared to controls. Decreased clearance in patients undergoing renal transplantation has also been reported for *d*-tubocurarine,[10] pancuronium,[11] pipecuronium,[12] and doxacurium.[13] Of the currently available muscle relaxants, only atracurium has a clearance not affected by renal failure and renal transplantation.[14,15]

The larger V_{SS} in renal transplant patients has been reported previously for pipecuronium.[12] A trend toward a larger V_{SS} in renal transplant patients has also been reported for vecuronium,[9] atracurium,[15] and doxacurium.[13] This larger V_{SS} likely results from one of two factors. First, although the renal transplant patients underwent hemodialysis before surgery, their extracellular fluid volume may be larger than that of normal patients. Second, during renal transplant surgery, we administer several liters of fluid before placement of the kidney to improve its function.[16,17] In the absence of measurements

TABLE 4. Values for the Derived Pharmacokinetic Parameters Obtained Using the Optimal Model

	Typical Value	Standard Error
V_{SS} ($ml \cdot kg^{-1}$)		
Normal renal function	207	14
Renal transplant	264	19
$t_{1/2}\pi$ (min)		
Normal renal function	2.2	0.3
Renal transplant	2.6	0.4
$t_{1/2}\alpha$ (min)		
Normal renal function	17.2	1.2
Renal transplant	22.1	1.8
$t_{1/2}\beta$ (min)		
Normal renal function	70.9	4.7
Renal transplant	97.2	17.3

TABLE 5. Neuromuscular Effects of a Bolus Dose of 600 $\mu g \cdot kg^{-1}$ Rocuronium in Patients with Normal Renal Function or Patients Undergoing Renal Transplantation

	Normal Renal Function	Renal Transplantation
Onset time (s)	69 ± 24 (46–125)	63 ± 17 (43–86)
Clinical duration (min)	47 ± 12 (36–64)	54 ± 22 (22–91)
Relaxation time (min)	93 ± 33 (64–151)	81 ± 34 (32–106)*
Recovery time (min)	29 ± 20 (13–67)	27 ± 11 (7–35)†

Values are mean ± SD; ranges are shown in parentheses. No statistical comparisons were performed (see text).
* n = 4.
† n = 5.

of extracellular fluid volume at various times during surgery in these patients, we are unable to estimate the relative contribution of these factors.

The need to administer supplemental muscle relaxants and the need for lower anesthetic concentrations in patients undergoing renal transplantation limited the quantity and comparability of data regarding the effects of renal failure and renal transplantation on the time course of neuromuscular blockade induced by rocuronium. Further clinical studies are necessary to address this important issue.

We did not observe any effect of perfusion of the transplanted kidney on plasma rocuronium concentration *versus* time curves, nor were we able to detect significant quantities of rocuronium in the urine produced by the transplanted kidney. Because it is possible that renal transplantation may induce other physiologic changes that alter rocuronium's elimination (*e.g.*, changes in hepatic blood flow), we cannot generalize our results to apply to patients with renal failure undergoing other types of surgery.

In conclusion, the pharmacokinetics and the onset of action of a $2 \times ED_{95}$ dose of rocuronium were not altered in patients with renal failure undergoing renal transplantation. In addition, the onset of action of rocuronium appears to be more rapid than that of other currently available nondepolarizing neuromuscular blocking drugs. Whether the results of the current study can be applied to patients with renal failure undergoing surgery other than renal transplantation is unknown. Our results suggest that rocuronium is a suitable drug for patients with renal failure undergoing renal transplantation and may be particularly desirable in these patients when rapid onset of neuromuscular blockade is needed.

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