

Effect of Renal Failure and Cirrhosis on the Pharmacokinetics and Neuromuscular Effects of Rapacuronium Administered by Bolus Followed by Infusion

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Background: **Recent trials indicate that rapacuronium's pharmacokinetic characteristics are influenced by both renal failure and cirrhosis but the time course of a single bolus dose of 1.5 mg/kg is affected minimally. The authors reassessed these pharmacokinetic findings and examined the time course of the same bolus dose followed by a 30-min infusion.**

Methods: **During nitrous oxide–isoflurane anesthesia, patients with normal renal and hepatic function (n = 25), those with renal failure (n = 28), and those with cirrhosis (n = 6) received a bolus dose of rapacuronium (1.5 mg/kg) followed by a 30-min infusion adjusted to maintain 90–95% twitch depression. At 25% recovery, neostigmine was administered. Blood was sampled until 8 h after the infusion to determine concentrations of rapacuronium and its active metabolite ORG9488. Rapacuronium's pharmacokinetic parameters were determined using mixed-effects modeling.**

Results: **Onset and facilitated recovery of twitch depression were similar in the three groups. Patients with renal failure required 22% less rapacuronium to maintain target twitch depression during the infusion. Rapacuronium's plasma clearance was 24% smaller in renal failure and decreased 0.5%/yr of age; rapid distribution clearance was 51% smaller in men than in women. After the infusion, ORG9488 concentrations decreased markedly more slowly in patients with renal failure. Cirrhosis did not alter the pharmacokinetics of rapacuronium.**

Conclusion: **Rapacuronium's plasma clearance and infusion requirement were decreased by renal failure. By dosing to maintain target twitch depression, recovery was not prolonged. Cirrhosis does not affect the pharmacokinetics or neuromuscular effects of rapacuronium. Persistence of ORG9488 in patients with renal failure might prolong recovery after rapacuronium if target twitch depression is not maintained or with administration of rapacuronium for more than 30 min. (Key words: Muscle relaxants.)**

RECENT clinical trials examined the effects of chronic renal failure[1] and cirrhosis[2] on the neuromuscular effects and pharmacokinetics of a single bolus dose of rapacuronium (Raplon, Organon Inc., West Orange, NJ), a nondepolarizing muscle relaxant with a rapid onset and short duration of action.[3] Although renal failure decreased the clearance of rapacuronium by 32% and of ORG9488 (its active metabolite) by 85%, the time course of neuromuscular effects differed minimally from that in healthy controls. In cirrhotic patients, clearance and steady state volume of distribution exceeded that in normal controls, but neuromuscular recovery did not differ between groups.

In both studies, only a single bolus dose of rapacuronium was administered and recovery occurred during the initial steep distribution phase. During these circumstances, the decreased clearance of rapacuronium and its metabolite in patients with renal failure and the larger volume of distribution of rapacuronium in cirrhotic patients did not affect rapacuronium's recovery profile adversely. However, with repeat dosing, as might occur with clinical use of rapacuronium,** the pharmacokinetic characteristics in patients with organ dysfunction might prolong recovery. In particular, persistence of rapacuronium's metabolite (which, based on plasma concentrations, is more potent than rapacuronium[4]) in renal failure might prolong recovery.

In the current study, we administered rapacuronium by bolus followed by a 30-min infusion to determine its neuromuscular effects, to confirm the pharmacokinetic findings reported previously,[1,2] and to examine whether the persistence of rapacuronium's metabolite affected its recovery profile.

Methods

The study was conducted at two sites: the University of California San Francisco and the University of Liverpool, United Kingdom. With local institutional review board approval and informed consent, 59 nonpregnant patients aged 18–65 yr were enrolled at the University of California San Francisco (n = 32) and at University of Liverpool (n = 27). Most patients underwent peripheral procedures; however, some patients with renal failure underwent abdominal procedures, such as placement of catheters for peritoneal dialysis or repair of incisional hernia. Patients were divided into three groups: healthy controls (normal renal and hepatic function, n = 25),

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** At present, rapacuronium is approved in the United States for administration as an initial bolus followed by up to three maintenance doses.

chronic renal failure (serum creatinine > 4.5 mg/dl, n = 28), and cirrhosis (Pugh-Child class A or B, n = 6). Patient weight was 76 ± 15 kg (mean ± SD) and did not differ between groups. Patients were not receiving any other drugs expected to influence the neuromuscular response to rapacuronium.

After an 8-h fast, patients were premedicated with 1 to 2 mg lorazepam orally or with 1 to 2 mg midazolam intravenously. After administration of 1–3 μg/kg fentanyl, anesthesia was induced with 3–5 mg/kg thiopental *via* an intravenous catheter placed in an upper extremity; anesthesia was then maintained with isoflurane (end-tidal concentration of 0.6%). An intravenous catheter was placed in the contralateral arm or in the external jugular vein (*e.g.*, if a vascular shunt was present in one arm) to sample blood. Ventilation was controlled to maintain normocapnia (end-tidal partial pressure of carbon dioxide [P_{CO_2}] of 30–35 mmHg). Esophageal temperature was maintained more than 36°C.

After loss of consciousness, supramaximal train-of-four (TOF) stimuli were applied to the ulnar nerve every 12 s. Mechanical twitch response of the adductor pollicis was measured with a calibrated force displacement transducer, amplified, and recorded on a strip chart. The first twitch response of each TOF (T1) was stable for more than 5 min before rapacuronium administration. The ratio of the fourth component to the first component of each TOF was determined.

Rapacuronium, 1.5 mg/kg, was administered over 5 s into a rapidly flowing infusion. When T1 recovered to 5% of control, rapacuronium (diluted to a concentration of 2.0 mg/ml) was infused for 30 min, starting at a rate of 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If twitch depression was outside of the range of 90–95%, the rapacuronium infusion rate was changed in increments no smaller than 8.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Each infusion rate was maintained for a minimum of 3 min. After the infusion was discontinued, twitch was permitted to recover spontaneously to 25% of control, at which time patients received 50 μg/kg neostigmine preceded by 10 μg/kg glycopyrrolate. In the first 11 patients at the University of California San Francisco (four healthy controls, five patients with renal failure, and two with cirrhosis), twitch was permitted to recover as long as clinically possible; if necessary, neostigmine and glycopyrrolate were administered to ensure complete neuromuscular recovery.

Venous blood, 5 ml, was sampled before and 2, 4, 7, and 10 min after the bolus dose and immediately before the start of the infusion. Additional samples were taken immediately before the end of the 30-min infusion and 2, 4, 7, 10, 20, 30, 45, 60, 75, 90, 120, and 150 min and 3, 4, 5, 6, 7, and 8 h after the infusion. At the University of California San Francisco, additional samples were taken at 10 and 20 min after the start of the infusion. Sodium dihydrogen phosphate was added to blood samples immediately to prevent degradation of rapacuronium. Blood was centrifuged within 30 min of sampling and plasma was stored at −20°C. Concentrations of rapacuronium and its primary 3-OH metabolite, ORG9488, were determined by Covance Laboratories (Madison, WI) using a high-performance liquid chromatography–mass spectometry (HPLC-MS) technique. The assay is linear for concentrations more than 2 ng/ml for both rapacuronium and ORG9488 and has a coefficient of variation of less than 11% for rapacuronium and less than 22% for ORG9488.

The pharmacokinetic characteristics of rapacuronium were determined using a population approach: mixed-effects modeling (NONMEM). Plasma concentration values for all subjects were analyzed simultaneously to determine typical values for the pharmacokinetic parameters, standard errors of these estimates, and interindividual variability. In addition, we determined the influence of renal function, cirrhosis, and other covariates (*e.g.*, demographic characteristics and preoperative laboratory values) on the pharmacokinetic parameters.[6]

Two-compartment models had the parameters clearance (Cl), distributional clearance ($CL_{distribution}$), and volumes of the central and peripheral compartments (V_1 and V_2, respectively). Three-compartment models had, in addition, a slow distributional clearance (CL_{slow}) and a volume of the deep peripheral compartment (V_3). $CL_{distribution}$ was renamed CL_{rapid}. Interindividual variability was permitted for each of these parameters and was assumed to have a log-normal distribution. Residual error between measured and predicted concentrations was initially assumed to have two components, one proportional to the predicted concentration (constant coefficient of variation), one additive; additional error models were tested.

A model-building approach was used. Initially, patients with renal failure and those with cirrhosis were assumed to have the same pharmacokinetic parameters as healthy controls. Two- and three-compartment models, both weight-normalized and non–weight-normalized, were compared to determine the appropriate structural model. Appropriateness of the error model was determined by visual inspection of the residual errors. After the population analysis was performed for each model, the NONMEM *post hoc* step was performed. This Bayesian step determines the parameter estimates for each individual in comparison with the population estimates. These differences are quantified through the NONMEM η (*eta*) terms. The resulting values for η were plotted against the covariates age, weight, height, gender, group (renal failure *vs.* cirrhosis *vs.* healthy controls), and preoperative values for hematocrit, hemoglobin, and serum concentrations of creatinine, creatinine clearance (estimated using the Cockcroft-Gault nomogram[7]), bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT). After a smoother (lowess, a local regression) was added to each plot, trends were sought by visual inspec-

Table 1. Neuromuscular Effects of Rapacuronium in Healthy Patients, in Patients with Renal Failure, and in Patients with Cirrhosis

	Healthy Controls	Patients with Renal Failure	Patients with Cirrhosis
Time (min) to			
Maximum twitch depression*	1.1 ± 0.2 (24)	1.3 ± 0.4 (27)	1.1 ± 0.3 (6)
Recovery of T1 to 5% of control (start of infusion)	15.4 ± 4.6 (25)	19.3 ± 8.2 (26)	14.0 ± 2.3 (6)
Rapacuronium dose administered during 30-min infusion (mg/kg)	1.49 ± 0.40 (25)	1.16 ± 0.40 (26)†	1.29 ± 0.31 (6)
Time (min) from			
End of infusion to 25% recovery of T1‡	13.4 ± 12.7 (21)	15.6 ± 10.0 (21)	8.5 ± 2.8 (4)
Neostigmine to TOF of 0.7‡	8.1 ± 5.4 (21)	7.6 ± 7.5 (20)§	6.6 ± 2.2 (4)

Values are mean ± SD, n in parentheses.

* Excludes two patients with delayed onset (peak twitch depression of 81% at 600 s in a healthy patient and > 98% twitch depression at 275 s in one renal failure patient). † Different from healthy controls ($P < 0.05$). ‡ Includes only those patients administered neostigmine at 25% recovery after discontinuation of the infusion of rapacuronium. § In one patient, neuromuscular monitoring was discontinued before TOF reached 0.7.

TOF = train-of-four.

tion. If a relation between a pharmacokinetic parameter and a covariate was observed, this relation was tested in the model. Additional parameters were accepted in the model if they improved the NONMEM objective function statistically (for $P < 0.01$, 6.6 units for one additional parameter, 9.1 units for two). Half-lives were calculated using standard formulas. The effect of renal failure and cirrhosis on plasma concentrations of ORG9488 was assessed visually.

Maximal twitch depression (expressed as percentage depression from the predrug control value), time from administration of rapacuronium to maximum twitch depression, and (for those patients who received rapacuronium by infusion) time to 5% recovery of T1 after the initial bolus dose were calculated. Total rapacuronium dose administered during the infusion was calculated. For those subjects who received neostigmine at 25% recovery after the infusion, time from end of the infusion to 25% recovery of T1 and time from neostigmine to recovery of the TOF ratio to 0.7 were determined. Values for the three groups were compared using analysis of variance or the Kruskal-Wallis test, followed by the Student-Newman-Keuls test. Values are reported as mean ± SD. $P < 0.05$ was considered statistically significant.

Results

Two patients with renal failure received only the bolus dose of rapacuronium and blood sampling was discontinued at 10 min because of technical difficulties; these patients are included in the pharmacokinetic analysis but not in the calculation of infusion rates and neuromuscular effects. In an additional nine patients (four healthy controls and five patients with renal failure), no blood was sampled; these patients are not included in the pharmacokinetic analysis.

In one healthy patient, maximum twitch depression was 81%; the remaining patients all developed 98% or more twitch depression. Time to peak twitch depression was 600 s in the patient who developed 81% twitch depression and 275 s in one renal failure patient. In the remaining patients, onset time was similar in the three groups (table 1). Time to 5% recovery of T1 (at which time the infusion was started) was similar in the three groups. The dose of rapacuronium infused over 30 min to maintain target twitch depression was 22% smaller in patients with renal failure than in healthy controls (fig. 1). After the end of the infusion, time to 25% recovery and time from neostigmine to recovery of a TOF ratio of 0.7 were similar for the three groups.

Plasma concentration data were obtained in 50 patients (of whom two received only the bolus dose). After the bolus dose, plasma concentrations of rapacuronium initially decreased rapidly in all groups (fig. 2). During the infusion, rapacuronium concentrations increased slightly and were similar in the three groups. After the infusion, plasma concentrations of rapacuronium initially decreased at a similar rate in the three groups. However, 8 h after the end of the infusion, rapacuronium concentrations were slightly larger in patients with renal failure than in the other groups (fig. 3), despite patients in renal failure receiving smaller doses.

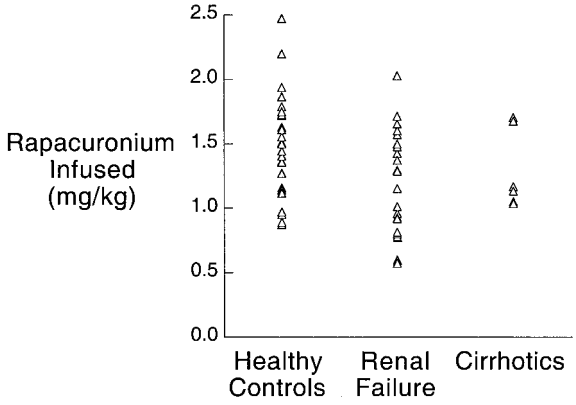

Fig. 1. Total rapacuronium doses administered during a 30-min infusion are shown for three groups; these values do not include the initial bolus dose of 1.5 mg/kg. The infusion rate was adjusted to maintain T1 at 5–10% of control.

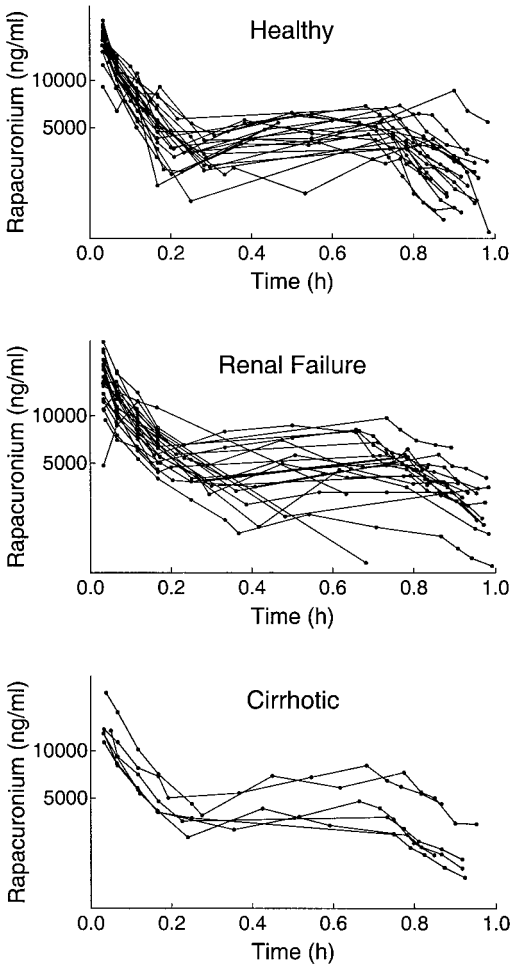

Fig. 2. Plasma concentrations of rapacuronium during the first h after bolus administration of rapacuronium are shown for three groups. When T1 reached 5% of control, rapacuronium was infused for 30 min.

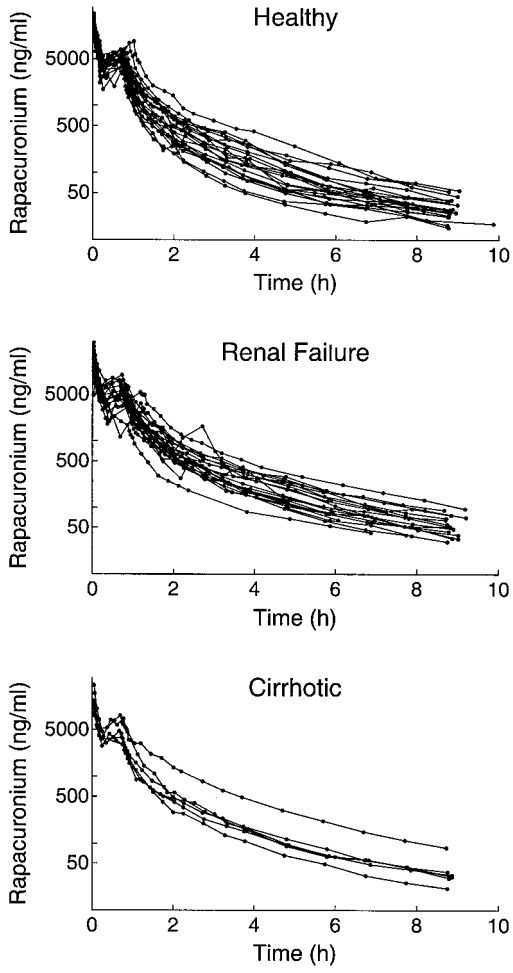

Fig. 3. Plasma concentrations of rapacuronium during the entire sampling period are shown for three groups. When T1 reached 5% of control, rapacuronium was infused for 30 min.

For rapacuronium, weight normalization improved the quality of fit of the two-compartment model (model 1 *vs.* model 2; table 2); therefore, weight normalization was adopted for subsequent analyses. A three-compartment model markedly improved the quality of fit (model 3 *vs.* model 1). Permitting interindividual variability in CL_{slow} to differ from that for CL_{rapid} and for V_3 to differ from that for V_2 further improved the quality of fit (model 4 *vs.* model 3). An error model with only a single component, a constant coefficient of variation, fit as well as one that also permitted an additive component (model 5 *vs.* model 4). Therefore, all subsequent models used weight-normalized pharmacokinetic parameters and permitted interindividual variability in each of these parameters; the error model contained only a single component.

With model 5, plots of *post hoc* η *versus* covariates suggested that patients with renal failure had a smaller clearance. Permitting the typical value of Cl to differ in patients with renal failure compared with the other groups improved the quality of the fit markedly (model 6 *vs.* model 5). With model 6, plots of *post hoc* η suggested that Cl decreased with age. Therefore, model 7 evaluated the effects of age on Cl using the following approach:

$$CL = THETA(1) \cdot (1 + AGEFACTOR \cdot (AGE - 45)) \quad (1)$$

$$CL = THETA(7) \cdot (1 + AGEFACTOR \cdot (AGE - 45)) \quad (2)$$

where CL is the typical value for a patient of a particular age, THETA(1) is the typical value for a normal or cirrhotic patient aged 45 yr, THETA(7) is the typical value for a renal failure patient aged 45 yr, 45 yr is the median age for the patients studied, and AGEFACTOR is estimated in the analysis. This model was statistically justified compared with the model in which age did not affect Cl (model 6); plots of *post hoc* η suggested that CL_{rapid} differed between genders. Permitting CL_{rapid} to differ between genders improved the quality of the fit (model 8 *vs.* model 7). *Post hoc* plots now suggested that V_2 was larger in cirrhotic patients, that CL_{slow} had both a weight-normalized and additive component, or that serum albumin concentration affected V_1. However, incorporating each of these into the pharmacokinetic

Table 2. Pharmacokinetic Models Tested

Model	Number of Compartments	Weight normalized	No. of ηs	No. of εs	Issue Tested	Objective Function
1	2	Yes	4	2	Weight normalization	14957.808
2	2	No	4	2	Weight normalization	14996.893
3	3	Yes	4	2	No. of compartments	14473.316
4	3	Yes	6	2	Model 3 + No. of ηs	14371.712
5	3	Yes	6	1	Model 4 + No. of εs	14371.906
6	3	Yes	6	1	Model 5 + different CL in renal failure	14236.868
7	3	Yes	6	1	Model 6 + age affects CL	14213.638
8*	3	Yes	6	1	Model 7 + gender affects CL_{rapid}	14147.113
9	3	Yes	6	1	Model 8 + V_2 differs for cirrhotics	14147.030
10	3	Yes	6	1	Model 8 + CL_{slow} has two components	14146.872
11	3	Yes	6	1	Model 8 + serum albumin affects V_1	14147.113

* Optimal model (see Results).

model failed to improve the quality of the fit further (models 9–11 compared with model 8). There was no evidence that incorporating serum creatinine or creatinine clearance into the model further improved the quality of fit.

Thus, the optimal model (table 3, fig. 4) for rapacuronium had three compartments and all pharmacokinetic parameters were weight-normalized. Clearance was 24% less in patients with renal failure than in the other groups. In all groups, Cl decreased 0.52%/yr of age compared with the value at age 45 yr (table 4). The coefficient of variation of the parameter estimate for the effect of age on Cl was 69%, suggesting that age might not influence Cl. However, a likelihood profile[8] (not shown) demonstrated that the decrease in Cl/yr of age was at least 0.3%. CL_{rapid} was 51% smaller in men than in women. Rapid and slow distribution half-lives were shorter in women than in men. Elimination half-life varied minimally as a function of gender, age, and renal function. There were no relation between the pharmacokinetic parameters and other covariates.

Plasma concentrations of ORG9488 were largest immediately after the bolus dose of rapacuronium in all groups, decreased rapidly, then increased during the rapacuronium infusion (fig. 5). After the infusion, plasma concentrations of ORG9488 decreased monotonically at a similar rate in healthy controls and in cirrhotic patients. In patients with renal failure, plasma concentrations of ORG9488 decreased minimally during the 8 h after the infusion (fig. 6). In one patient with cirrhosis, the time course of ORG9488 was similar to that of patients with renal failure; this patient's serum creatinine was 2.3 mg/dl.

Discussion

We found that the clearance of rapacuronium was 24% less in patients with renal failure than in normal patients and those with cirrhosis. As a result, doses of rapacuronium required to maintain a target range of neuromuscular depression were smaller in patients with renal failure. The magnitude of decrease in the clearance in renal failure in the current study is similar to that reported previously by Szenohradszky *et al.*[1] (32%) in a similar group of patients aged 18–45 yr. Patients with renal failure studied by Szenohradszky *et al.*[1] did not have a longer median time to 25% recovery of T1 or to a TOF ratio more than 0.7. However, a few of their nine patients with renal failure had prolonged recovery, a finding that would be accentuated if supplemental doses of rapacuronium were administered. Thus, our finding that rapacuronium infusion requirements are decreased by renal failure is consistent with the findings reported

Table 3. Pharmacokinetic Parameters Estimated in the Optimal Model (Model 8)

	Typical Value	Standard Error	Interindividual Variation* (%)
Cl (ml · kg^{-1} · min^{-1})			
Normal, cirrhosis	6.74 · (1 − 0.0052 · (age − 45))	0.451, 0.00353†	26
Renal failure	5.14 · (1 − 0.0052 · (age − 45))	0.638, 0.00353‡	26
V_1 (ml/kg)	63.2	4.2	36
CL_{rapid} (ml · kg^{-1} · min^{-1})			
Women	5.71	1.04	35
Men	2.79	0.26	35
V_2 (ml/kg)	82	7.38	41
CL_{slow} (ml · kg^{-1} · min^{-1})	1.14	0.0715	38
V_3 (ml/kg)	158	11.1	36

* Computed as 100% · $\sqrt{\omega^2}$; where ω^2 = variance (η); 68% of the population lies within this range of the typical value. † Value 0.451 applies to value 6.74; value 0.00353 applies to value 0.0052. ‡ Value 0.638 applies to value 5.14; value 0.00353 applies to value 0.0052.

Table 4. Clearance and Half-lives Estimated from the Optimal Model (Model 8)

Group	Gender	Parameter	Age (yr) 20	30	40	45	50	60
Healthy controls, cirrhotic patients	Male	Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	7.62	7.27	6.92	6.74	6.56	6.21
		$t_{1/2}\pi$ (min)	3.6	3.7	3.8	3.8	3.9	4.0
		$t_{1/2}\alpha$ (min)	27.8	28.1	28.5	28.7	28.9	29.3
		$t_{1/2}\beta$ (min)	113	114	115	115	116	117
Healthy controls, cirrhotic patients	Female	Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	7.62	7.27	6.92	6.74	6.56	6.21
		$t_{1/2}\pi$ (min)	2.6	2.7	2.7	2.8	2.8	2.9
		$t_{1/2}\alpha$ (min)	18.5	18.9	19.3	19.5	19.8	20.3
		$t_{1/2}\beta$ (min)	112	113	114	115	115	117
Renal failure	Male	Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	5.81	5.54	5.27	5.14	5.01	4.74
		$t_{1/2}\pi$ (min)	4.2	4.3	4.4	4.4	4.5	4.6
		$t_{1/2}\alpha$ (min)	29.9	30.3	30.7	30.9	31.1	31.6
		$t_{1/2}\beta$ (min)	119	120	121	122	123	125
Renal failure	Female	Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	5.81	5.54	5.27	5.14	5.01	4.74
		$t_{1/2}\pi$ (min)	2.9	3.0	3.0	3.0	3.0	3.1
		$t_{1/2}\alpha$ (min)	20.9	21.4	21.9	22.2	22.5	23.1
		$t_{1/2}\beta$ (min)	118	120	121	122	122	124

$t_{1/2}\pi$ = rapid distribution half-life; $t_{1/2}\alpha$ = slow distribution half-life; $t_{1/2}\beta$ = elimination half-life.

by Szenohradszky *et al.*[1] The combined results of these studies suggests that rapacuronium's recovery profile after a single dose or a bolus dose followed by a 30-min infusion adjusted to maintain target twitch depression is usually not affected by renal function.

In cirrhotic patients, rapacuronium's clearance did not differ from that in healthy adults. This finding conflicts with that of Duvaldestin *et al.*[2] who reported that rapacuronium's clearance was larger in cirrhotic patients (median: 6.9 $ml \cdot kg^{-1} \cdot min^{-1}$; range: 6.1–8.9 $ml \cdot kg^{-1} \cdot min^{-1}$) than in healthy controls (median: 5.3 $ml \cdot kg^{-1} \cdot min^{-1}$; range: 4.2–8.4 $ml \cdot kg^{-1} \cdot min^{-1}$). Duvaldestin *et al.*[2] also reported that rapacuronium's steady state distribution volume was 50% larger in cirrhotic patients than in healthy controls, whereas we observed no effect of cirrhosis on distribution volume. As in the current study, neuromuscular recovery was similar in patients with cirrhosis compared with healthy controls. The cirrhotic patients in the two studies appear to be similar: the diagnosis of cirrhosis was typically confirmed by liver biopsy and patients had similar Pugh-Child scores (5–9 in the current study, 5–10 in the Duvaldestin *et al.*[2] study). Regardless, these studies suggest that cirrhosis does not prolong the duration of action of rapacuronium either as a single bolus dose or as a bolus followed by a 30-min infusion and that rapacuronium dosing in cirrhotic patients should probably be similar to that in healthy patients. However, the number of cirrhotic patients investigated in both studies is small so that additional pharmacokinetic studies may be needed in this patient population.

We also observed that rapacuronium's clearance decreased with age. This finding is similar to that of Szenohradszky *et al.*[1] who reported that Cl decreased 0.9%/yr (compared with Cl at age 30 yr) in a group of volunteers and patients aged 18–45 yr. In contrast, Fisher *et al.*[9] reported that age did not affect Cl in a group of patients aged 24–83 yr. The major difference between the single study that did not demonstrate an effect of age and those that did is the duration and intensity of blood sampling: the two studies that demonstrate an effect of age sampled for 8 h or more and obtained more than 15 samples/patient; the study that did not demonstrate an effect of age sampled for less than 4 h and obtained only 3 to 4 samples/patient. It is likely that the limited duration of sampling in the one study prevented the investigators from identifying an age-related effect that was not apparent during the initial several hours of sampling.

The other major finding of the current study is that elimination of rapacuronium's active metabolite ORG9488 is markedly delayed in patients with renal failure. When Szenohradszky *et al.*[1] gave a single 1.5-mg/kg dose of rapacuronium to patients with renal failure, plasma concentrations of ORG9488 persisted in the range of 200 ng/ml for 8 h. In the current study, in which the total rapacuronium dose averaged 2.66 mg/kg in patients with renal failure, plasma concentrations of ORG9488 also persisted for 8 h after the final administration of rapacuronium and were proportionally larger than those in the previous study. This finding in patients with renal failure contrasts to that in healthy patients and in all but one of those with cirrhosis in whom plasma concentrations of ORG9488 decrease consistently when rapacuronium is no longer administered. The cirrhotic patient who had persistent concentrations of ORG9488 had an abnormal serum creatinine but did not meet our criteria for renal failure; this emphasizes the impact of renal dysfunction on the elimination of ORG9488.

The importance of persistent concentrations of ORG9488 results from its potency—a study by Schiere *et al.*[4] suggests that, based on steady state plasma concen-

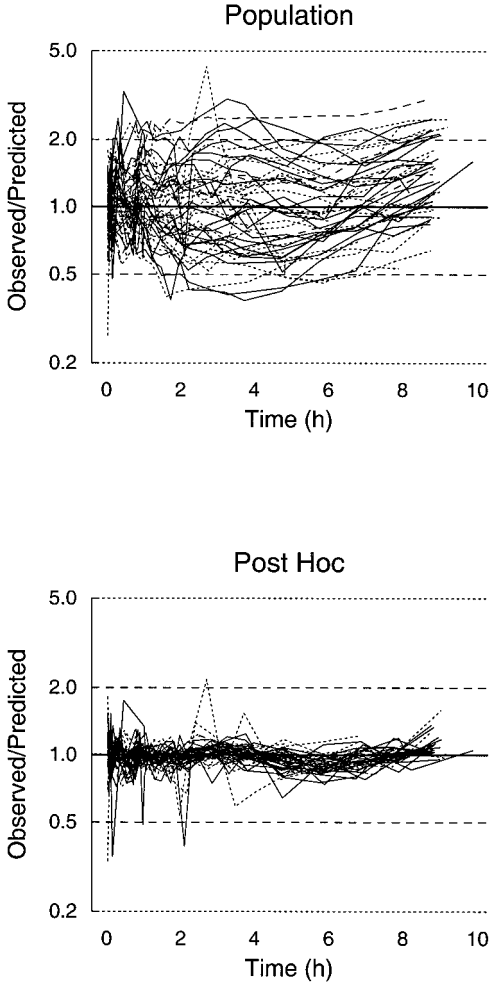

Fig. 4. Quality of fit of the pharmacokinetic model to the values for plasma concentration of rapacuronium. The *x*-axis is time (min) after administration of the bolus dose of rapacuronium. The *y*-axis is the ratio of the measured concentration of rapacuronium to the value predicted by the population pharmacokinetic model (*top*) or the *post hoc* fit (*bottom*). Each line represents values from a single individual. Healthy controls (N = 21) are shown with a solid line, patients with renal failure (N = 23) with a dotted line, and patients with cirrhosis (N = 6) with a dashed line. If the model fit the data perfectly, all lines would lie horizontally at 1.0. The improved quality of fit of the *post hoc* values compared to those from the population model is expected in that the *post hoc* model permits interindividual variability, whereas the population model does not.

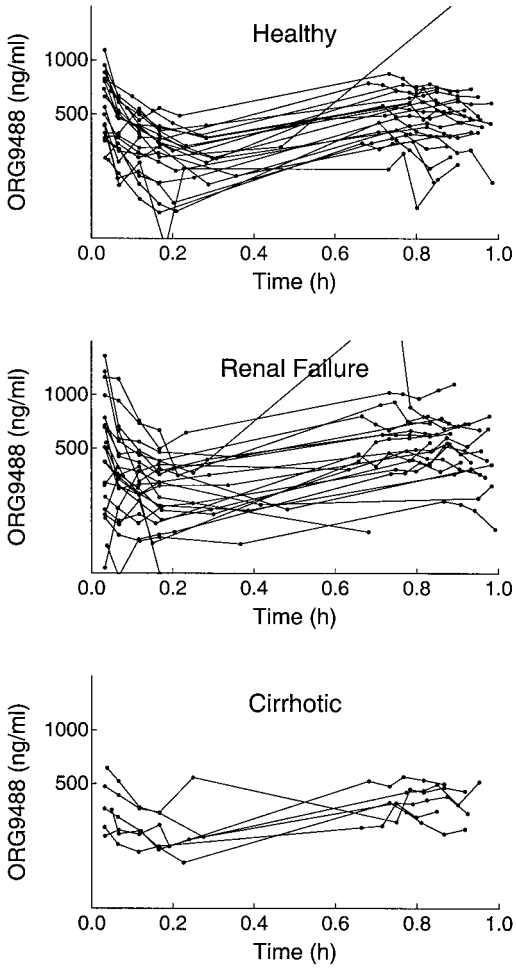

Fig. 5. Plasma concentrations of ORG9488 during the first h after bolus administration of rapacuronium are shown for three groups. When T1 reached 5% of control, rapacuronium was infused for 30 min.

trations, ORG9488 is 2 to 3 times as potent as rapacuronium. The typical concentration of ORG9488 attained in renal failure patients in the current study, approximately 500 ng/ml, is approximately one fourth of the concentration that Schiere *et al.*[4] calculated would produce 50% twitch depression at steady state. Thus, persistence of ORG9488 for many hours after rapacuronium administration might place a patient with renal dysfunction at risk for prolonged weakness in clinical practice. The mode of rapacuronium administration in the current study—adjustment of the infusion rate to maintain twitch tension at 5–10% of control—resulted in patients with renal failure receiving smaller rapacuronium doses than in the other groups and permitted rapid facilitated recovery. Had we dosed rapacuronium at the same rate in all groups, plasma concentrations of both rapacuronium and ORG9488 would have been larger in renal failure patients than in the other groups. In turn, paralysis may have been prolonged by renal failure. However, adjusting the rapacuronium dose minimized the impact of renal failure on accumulation of ORG9488.

Finally, we observed that spontaneous recovery of neuromuscular function to 25% of control and facilitated recovery to a TOF ratio of 0.7 were similar in the three groups. This finding is expected in patients with cirrhosis in whom plasma concentrations of rapacuronium and ORG9488 typically follow a time course similar to that in normal patients. However, we speculate that the decreased Cl of rapacuronium and the markedly prolonged elimination of ORG9488 in patients with renal failure might impair the rate of both spontaneous and facilitated recovery if supplemental rapacuronium is administered without maintaining target twitch depression or if rapacuronium is dosed for more than 30 min.

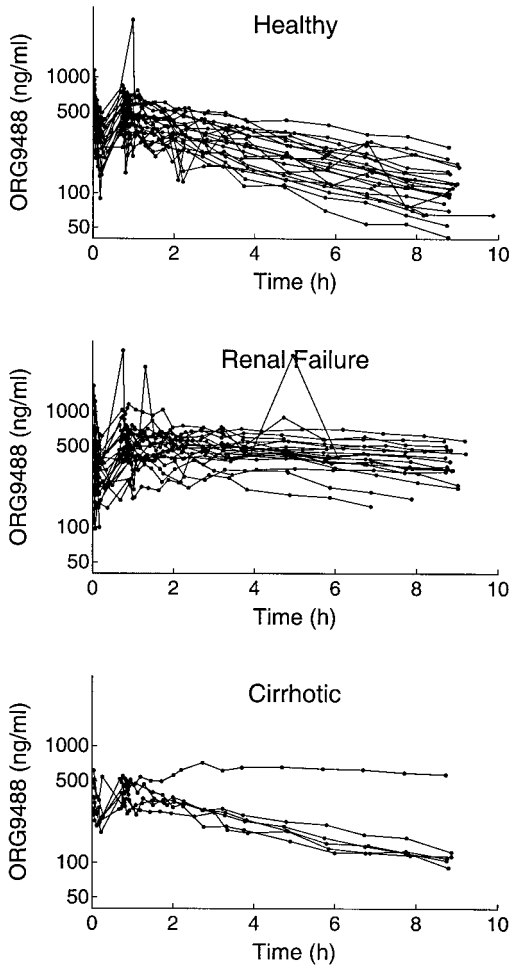

Fig. 6. Plasma concentrations of ORG9488 during the entire sampling period are shown for three groups. When T1 reached 5% of control, rapacuronium was infused for 30 min.

In the current study, we did not model the pharmacodynamics of rapacuronium. Such modeling depends on accurate data regarding the relative potency and the equilibration rate constant for rapacuronium's active metabolite compared with rapacuronium. Although Schiere *et al.*[4] reported the pharmacokinetic characteristics of rapacuronium and its active metabolite, their large variability in the potency of both compounds (*e.g.*, a fourfold range of potency values for ORG9488) limits applicability of simulations based on average potency values. Had Schiere *et al.*[4] performed a crossover study in which volunteers received rapacuronium on one occasion and ORG9488 on another, we might have had sufficient information to model the impact of renal failure and cirrhosis on dose requirements of rapacuronium. However, the results of the current analysis are consistent with our clinical finding that renal failure decreases the infusion requirement for rapacuronium.

A second limitation of the current study is that the number of cirrhotic patients was small, a result of difficulty in recruiting sufficient candidates at the two sites. However, the findings in cirrhotic patients are similar to those in a previous study.

In summary, we confirm that rapacuronium's Cl is decreased in patients with renal failure. In addition, we confirm our finding that rapacuronium's Cl decreases with age. Unlike Duvaldestin *et al.*,[2] we found no effect of cirrhosis on rapacuronium's Cl or volume of distribution in a small cohort of patients. Finally, as in previous studies, we observed that elimination of rapacuronium's active metabolite ORG9488 is markedly delayed in patients with renal failure. Our findings indicate that rapacuronium dosing is not affected by cirrhosis but that its maintenance requirement is decreased in patients with renal failure.

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