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Pharmacokinetics of Rocuronium during the Three Stages of Liver Transplantation

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Background: **Little is known about the influence of liver transplantation on the pharmacokinetics of most anesthetic drugs. The authors determined the pharmacokinetics of rocuronium during liver transplantation and examined whether variability in pharmacokinetics could explain variability in recovery of neuromuscular function.**

Methods: **Twenty patients undergoing liver transplantation were given rocuronium, 600 μg/kg, after induction of anesthesia and again after perfusion of the transplanted liver. Plasma was sampled to determine rocuronium concentrations. Pharmacokinetic models were fit to rocuronium concentrations *versus* time data using a mixed-effects population approach. Various models permitted changes in clearance (Cl) or central compartment volume to account for changes in hepatic function and circulatory status during the paleohepatic, anhepatic, and neohepatic periods. Time to initial recovery of four twitches of the orbicularis oculi was determined.**

Results: **During the paleohepatic and anhepatic periods, the typical value of Cl was 2.47 $ml \cdot kg^{-1} \cdot min^{-1}$ and was not influenced by the magnitude of preexisting liver disease (as evidenced by prothrombin time, bilirubin, serum albumin, alanine transaminase [ALT], and aspartate transaminase [AST]). During the neohepatic period, the typical value of Cl varied as a function of the duration of warm ischemia of the hepatic allograft and was 2.72 $ml \cdot kg^{-1} \cdot min^{-1}$ for a patient with an average 60-min period of warm ischemia; time to neuromuscular recovery varied as a function of Cl.**

Conclusions: **Despite prolonged hypothermic ischemia, the newly transplanted liver eliminates rocuronium as well as the diseased native liver (and comparably with historical control values). However, some patients had decreased rocuronium Cl during the neohepatic period, apparently a result of prolonged graft warm ischemia. The authors' finding of preservation of hepatic drug elimination in the hepatic allograft is consistent with limited data for other drugs evaluated during anesthesia. (Key words: Liver: transplantation, disease. Neuromuscular relaxants: rocuronium. Pharmacokinetic modeling: population techniques, NONMEM.)**

DESPITE the increasing frequency of liver transplantation, relatively little is known about the influence of removal of the native liver and perfusion of the transplanted liver on the pharmacokinetics of drugs given during anesthesia. Metabolism of lidocaine to its major metabolite, monoethylglycinexylide (MEGX), has been proposed as a marker of hepatic function of donor livers before harvesting.[1] A readily available approach, duration of clinical effect of drugs metabolized by the liver, has been proposed as an indicator of primary graft dysfunction after liver transplantation. For example, Lukin *et al.*[2] administered vecuronium, 100 μg/kg, at the beginning of the neohepatic period: in those 17 patients whose liver functioned after transplantation, neuromuscular recovery (time to appearance of four components of the train-of-four response to facial nerve stimulation) averaged 113.5 ± 9.0 min (mean ± SD); however, in those five patients with primary dysfunction, neuromuscular recovery occurred at 165.4 ± 27.3 min ($P < 0.05$). Subsequently, Marcel *et al.*[3] demonstrated that prolonged neuromuscular recovery from rocuronium also identified patients with primary liver dysfunction. Based

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Table 1. Demographic Information about the 20 Patients Who Underwent Liver Transplantation and Their Donor Livers

	All Patients	Patients Who Developed Primary Graft Dysfunction
N	20	2
Age (yr)	53 ± 8	41, 68
Weight (kg)	75 ± 17	62, 54
Height (cm)	170 ± 16	162, 140
Gender	10 males, 10 females	Male, female
Total duration of graft ischemia (min)	509 ± 170	410, 717
Duration of warm graft ischemia (min)	68 ± 19	74, 97

Values for "All Patients" are mean ± SD; individual values are shown for patients with primary graft dysfunction.

on these two trials with muscle relaxants, these investigators suggested that primary graft dysfunction could be detected intraoperatively based on a prolonged response to certain muscle relaxants eliminated by the liver. However, neither study correlated duration of neuromuscular effect during liver transplantation with pharmacokinetics of the muscle relaxant.

In the present study, we determined the pharmacokinetics of rocuronium given twice during liver transplantation, once after induction of anesthesia and again after perfusion of the transplanted liver. This design permitted examination of the influence of physiologic changes during liver transplantation (total hepatectomy, absent hepatic function and circulatory changes during the anhepatic period, reperfusion of the hepatic allograft) on rocuronium's pharmacokinetics and the relationship between changes in pharmacokinetics and rocuronium's duration of action. Because rocuronium is believed to be eliminated mainly by the liver,[4,5] we anticipated that rocuronium's pharmacokinetics may be altered during each of the periods of liver transplantation. For example, end-stage liver disease may decrease clearance in the paleohepatic period; absence of the liver during the anhepatic period may be associated with a marked decrease in clearance, and the effects of prolonged hypothermic preservation may alter elimination during the neohepatic period.

Methods

Patients in the present study are a subset (the final 20) of the 57 patients reported by Marcel *et al.*[3] The protocol was approved by the institutional review board of Baylor University Medical Center, and informed consent was obtained from 20 patients aged 41–68 years with end-stage liver disease undergoing orthotopic liver transplantation at that medical center (tables 1, 2). Child's class was A in 6 patients, B in 11, and C in 3. Ascites was absent or minimal in 11 patients, moderate in 6, and severe in 3. Thirteen of the patients had normal neurologic status; the remainder had mild-to-moderate encephalopathy. Total blood loss during surgery was 2.0 ± 1.6 l; during the paleohepatic and anhepatic periods, blood loss was 0.7 ± 0.7 l and 0.5 ± 0.4 l, respectively. Despite the presence of end-stage liver disease, all patients were clinically stable preoperatively, and none had fulminant hepatic failure. Venovenous bypass was used in 12 patients at the discretion of the surgeon. Time from administration of the initial dose of rocuronium to the anhepatic period was 129 ± 43 min (range, 30–214 min); the anhepatic period lasted 68 ± 19 min (range, 40–123 min). Two patients developed posttransplantation primary graft dysfunction, manifested by values of alanine transaminase (ALT) and aspartate transaminase (AST) > 2000 U/l and prothrombin time > 16 s within 3 days of surgery. Additional details of the clinical course and anesthetic treatment of these patients have been described previously.[3]

Anesthesia was induced with thiopental (4.7 ± 1.5 mg/kg) and fentanyl (4.5 ± 2.1 μg/kg) and maintained with isoflurane (0.3–0.8% end-tidal concentrations) and fentanyl (15 ± 11 μg/kg). Immediately after induction of anesthesia, rocuronium, 600 μg/kg, was given as an intravenous bolus to facilitate tracheal intubation (paleohepatic dose). A second 600 μg/kg dose of rocuronium was given 3–25 min after perfusion of the donor liver (neohepatic dose). After induction of anesthesia (but before rocuronium administration), the facial nerve was stimulated *via* cutaneous electrodes with a peripheral nerve stimulator (MiniStim MS-II,< Life Tech, Inc.,

Table 2. Values for Hepatic Function and Injury in the Preoperative Period for 20 Patients Who Underwent Liver Transplantation

	Mean ± SD	Range
Prothrombin time (s)	14.6 ± 3.4	11.4–25.1
Bilirubin (mg/dl)	7.5 ± 10.2	0.7–38.0
Albumin (g/dl)	3.1 ± 0.6	1.7–4.1
AST (U/L)	1,590 ± 2,454	130–11,445
ALT (U/L)	894 ± 837	66–3,633

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

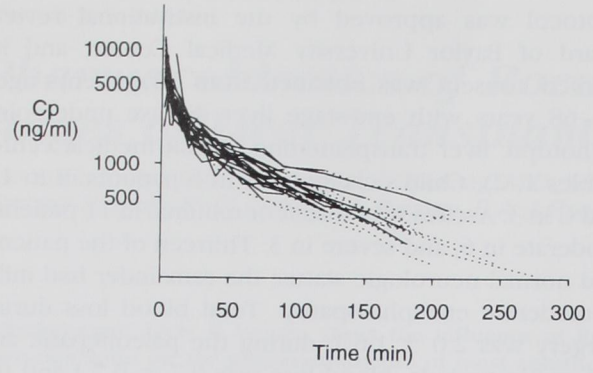

Fig. 1. Time course of plasma concentration of rocuronium, 600 μg/kg, given during the paleohepatic period in 20 patients undergoing liver transplantation. The *x* axis is time; the *y* axis is (log) rocuronium concentration. Each line is from a single individual; the *solid section* represents the paleohepatic period; the *dotted section* the anhepatic period.

Houston, TX). Two-Hz train-of-four stimuli were applied every 20 s. Resulting contractions of the orbicularis oculi muscle were counted by an anesthesiologist and an investigator every 5 min until three responses were observed and then every 2 min until four responses were observed. This same monitoring sequence was applied after the second rocuronium dose. Duration of action of each dose of rocuronium was defined as the time from rocuronium administration until initial appearance of the fourth response of the train-of-four.

Arterial blood samples (5 ml each) were obtained before each dose of rocuronium and at frequent intervals from 2–277 min after the first dose of rocuronium (fig. 1) and 2–210 min after the second dose of rocuronium (fig. 2). The number of samples ranged from 14–20 after the first rocuronium dose and 11–18 after the second dose. Blood was buffered and then centrifuged, and plasma was stored immediately at −70°C until analysis. Plasma concentrations of rocuronium (Cp) were determined by gas chromatography[6] at the University of California. The assay is sensitive to rocuronium concentrations of 10 ng/ml with a coefficient of variation of 10% at a concentration of 20 ng/ml.

The pharmacokinetics of rocuronium were determined at the University of California using a population approach,[7] *i.e.,* values for all subjects were analyzed simultaneously to yield estimates for "typical values" of the pharmacokinetic parameters and interindividual variability. The analysis was performed using the NONMEM program.†† Most analyses were performed using a new option of NONMEM (not available in the publicly distributed version) that assures that the distribution of individual values for the pharmacokinetic parameters is centered at the typical value; this overcomes a problem encountered by Kataria *et al.*[8] when NONMEM was used to fit datasets in which many samples were obtained from each subject.

Parameters for the two-compartment model were volume of the central compartment (V_1), volume of the peripheral compartment (V_2), clearance (Cl, equal to $V_1 \cdot k_0$), and distribution clearance ($Cl_{distribution}$, equal to $V_1 \cdot k_{12}$) where k_0 is the elimination rate constant and k_{12} is the rate constant for movement of rocuronium from the central to the peripheral compartment. The three-compartment model had two additional parameters: volume of the third (deep) compartment (V_3) and slow distribution clearance (Cl_{slow}, clearance equal to $V_1 \cdot k_{13}$), where k_{13} is the rate constant for movement of rocuronium from the central to the deep compartment. Volume of distribution at steady state (V_{ss}) was equal to V_1 plus V_2 (plus V_3, if appropriate). For the two-compartment model, distribution and elimination half-lives ($t_{1/2}\alpha$ and $t_{1/2}\beta$, respectively) were determined using standard equations.[9] For the three-compartment model, distribution ($t_{1/2}\pi$ and $t_{1/2}\alpha$) and elimination half-lives were determined iteratively.‡‡

Variability between subjects was modeled by expressing the pharmacokinetic parameters of each subject as a function of the typical value for the population and a factor for that subject. Because interindividual variabil-

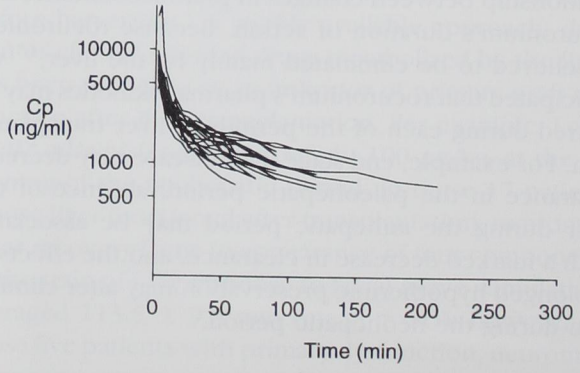

Fig. 2. Time course of plasma concentration of rocuronium, 600 μg/kg, given during the neohepatic period in 20 patients undergoing liver transplantation. The *x* axis is time; the *y* axis is (log) rocuronium concentration. Each line is from a single individual.

†† Beal SL, Sheiner LB: NONMEM User's Guide, San Francisco, University of California, 1992.

‡‡ Excel Solver,® Microsoft, Redmond, WA.

ity tends to assume a log-normal (*i.e.,* skewed) distribution, interindividual variability for Cl was modeled as:

$$\ln(Cl_i) = \ln(Cl) + \eta_i \quad (1)$$

where Cl_i is the estimate for Cl for the i-th individual, Cl is the typical value for the population, and η_i is a random variable with mean 0.0 and variance ω^2. All models permitted interindividual variability in each of the pharmacokinetic parameters. For the three-compartment model, interindividual variability was assumed to be the same for V_2 and V_3 and for $Cl_{distribution}$ and Cl_{slow}. In some models, interindividual variability was permitted to differ during the times at which the native and the transplanted liver were being perfused (the paleohepatic and neohepatic periods, respectively). Residual error between predicted and observed concentrations was assumed to have two components: one proportional to the predicted value and the other one constant. This "error model" is designed to replicate the situation in which error in an assay is approximately proportional to the predicted concentration until the concentration approaches the assay's limit of detection.

We expected that physiologic changes during surgery would influence distribution or elimination of rocuronium, and we tested various pharmacokinetic models incorporating these physiologic changes, *e.g.,* permitting step changes in pharmacokinetic parameters at the initiation of the anhepatic period or at the time that the new liver was perfused. Models that required additional terms (called θ's in NONMEM parlance) were accepted only if they significantly improved the pattern of residual differences between observed and predicted values and the objective function ($P < 0.01$, *e.g.,* a model with one additional θ improved the objective function by 6.6). For example, using data from only the first dose of rocuronium, we tested two models, one in which Cl was the same during the paleohepatic and anhepatic periods and a second in which Cl was permitted different values during these two periods. Because the latter model contained more parameters (*i.e.,* two values for Cl compared with a single value in the alternate model), it was accepted only if statistically justified.

For each model, we determined the differences between individual parameter estimates (determined using the NONMEM *post hoc* step) and "typical" values (determined from NONMEM's population fit). These differences were plotted against each of the covariate's gender, age, weight, height, blood loss, and preoperative measures of hepatic and renal function (bilirubin, albumin, AST, ALT, prothrombin time, glomerular filtration rate); trends were sought by plotting a smoother (Supersmoother§§) through these data and examining for a systematic deviation of this smoother from the horizontal line with zero elevation. If these plots suggested a relationship existed between a covariate and a pharmacokinetic parameter, we tested an additional model incorporating the covariate (for an example, see Results section).

Initial pharmacokinetic analyses were performed using Cp data from the first dose only. First, we evaluated whether normalizing all pharmacokinetic parameters to the subject's body weight improved the pharmacokinetic fit, and we compared the fits resulting from the two- and three-compartment models. Next, we examined the influence of preexisting liver disease (as assessed by preoperative values of prothrombin time, bilirubin, albumin, AST, or ALT) or renal dysfunction (as assessed by preoperative glomerular filtration rate), patient demographics (age, height, weight, gender), and blood loss on the pharmacokinetic parameters. The effect of total hepatectomy was evaluated by testing models in which typical values of Cl or V_1 were permitted step changes at initiation of the anhepatic period (the time at which the hepatic inflow was stopped). We also tested a model in which the step change in Cl at initiation at the anhepatic period could differ between patients with and without venovenous bypass.

Because the analysis suggested that Cl was the same during the paleohepatic and anhepatic periods (see Results section), we performed a sensitivity analysis to determine the magnitude of change in Cl that could be detected based on our study design and sampling regimen. Pharmacokinetic analyses were performed in which $Cl_{anhepatic}$ was fixed at 75–100% of $Cl_{paleohepatic}$. We then determined the smallest percentage difference between $Cl_{anhepatic}$ and $Cl_{paleohepatic}$ that increased the objective function significantly compared with the model in which $Cl_{anhepatic}$ and $Cl_{paleohepatic}$ were identical.

The second set of analyses were performed using Cp data from both doses, *i.e.,* calculations for the second dose accounted for residual rocuronium from the first dose. First, the model determined from the previous analyses was used to describe the Cp data during the paleohepatic, anhepatic, and neohepatic periods. Then, we tested the influence of the transplanted liver by permitting step changes in the typical values of Cl or V_1

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

at the time at which the transplanted liver was perfused (start of the neohepatic period). We also permitted interindividual variability in Cl or V_1 to differ during the neohepatic period compared with earlier periods. Finally, we examined the influence of the duration of total ischemia (from clamping of hepatic inflow in the donor to reperfusion in the recipient) or warm ischemia (from removal of the donor liver from its hypothermic environment to reperfusion in the recipient), and demographic factors in the donor (age, height, weight, gender) on Cl during the neohepatic period.

Once the "optimal" pharmacokinetic model was selected, we calculated the percent error (PE = [predicted − measured]/predicted, expressed in %) and the absolute percent error for each plasma concentration from that model. The median percent error and median absolute percent error were then determined.

To evaluate whether pharmacokinetic differences explained differences between subjects in the duration of action of rocuronium, we plotted individual values for Cl during the paleohepatic and neohepatic periods (determined from the optimal model using NONMEM's *post hoc* step) against duration of action of the corresponding dose of rocuronium.

Statistical comparisons for the NONMEM analyses were performed using the likelihood ratio test;[10] $P < 0.01$ was required for statistical significance. Other comparisons used analysis of linear regression or Student's *t* test for unpaired or paired data; a $P < 0.05$ was required for statistical significance. Values are reported as mean ± SD unless otherwise indicated.

Results

Of the 615 plasma samples used to determine rocuronium concentration, four (from three patients) were not used in the analysis. One subject had Cp values of 676, 429, and 389 ng/ml at 90, 120, and 150 min, respectively, after the first rocuronium dose, and then values of 129 and 142 ng/nl at 180 and 210 min, respectively (the latter two values being obtained during the anhepatic period). A second patient had a single, similarly aberrant value during the anhepatic period. The third patient had a twofold increase in rocuronium concentration between samples obtained 75 and 90 min after the second dose of rocuronium. The unexpected changes in these Cp values compared with previous values suggested physiologic events (*e.g.,* acute massive blood loss and the resulting hemodilution) that could not be modeled adequately in the pharmacokinetic analysis.

Pharmacokinetics of the first dose of rocuronium

With two- and three-compartment models, permitting pharmacokinetic parameters to be weight-adjusted markedly improved the quality of the fit (table 3, models 1–4). Compared with a two-compartment model, the three-compartment model was associated with a marked improvement in the quality of the fit of the model to the data and a marked decrease in the objective function. Therefore, all subsequent analyses had three compartments, and pharmacokinetic parameters were weight-normalized. Plots of pharmacokinetic parameters for each subject (determined using NONMEM's *post hoc* step) against covariates (demographics, preoperative markers of hepatic and renal function) suggested that the typical values of V_1 decreased with age. This observation was incorporated into the model as follows:

$$V_1(\text{individual}) = V_1(\text{typical}) \cdot (1 + (\text{Age} - 50) \cdot \text{AgeFactor}) \quad (2)$$

where 50 yr is approximately the average age of the patients, and AgeFactor is determined in the analysis. This model (5) fit the data better than a model in which the typical values for weight-adjusted V_1 were the same for all subjects. Covariate plots also suggested a relationship between Cl and preoperative albumin concentration. However, a model incorporating albumin into individual values for Cl failed to improve the quality of the fit (model 6).

The effect of physiologic changes resulting from total hepatectomy was examined in several models. Model 5, in which pharmacokinetic parameters did not change through the paleohepatic and anhepatic periods, fit the data well during both periods. A model (7) in which Cl changed acutely at initiation of the anhepatic period (*i.e.,* different values of Cl during the two periods) suggested that $Cl_{anhepatic}$ was 95% of $Cl_{paleohepatic}$. However, the objective function for this model was not better than that for model 5, in which Cl was the same during these two periods, *i.e.,* it was not justified statistically. Sensitivity analysis demonstrated that a 25% decrease in $Cl_{anhepatic}$ compared with $Cl_{paleohepatic}$ could have been detected.

Permitting the typical value of V_1 to change acutely at initiation of the anhepatic period did not improve the quality of fit of the model (8) to the data, nor did

Table 3. Pharmacokinetic Analyses Using Data from the First Dose of Rocuronium

Model No.	Issue Tested	Objective Function	Statistical Significance
1	Two compartments, parameters not weight-adjusted	4188.6	—
2	Two compartments, parameters weight-adjusted	4139.6	Preferred over model 1*
3	Three compartments, parameters not weight-adjusted	4087.5	$P < 0.05$ *vs.* model 1
4	Three compartments, parameters weight-adjusted	4046.2	$P < 0.05$ *vs.* model 2; preferred over model 3*
5	Model 4 plus V_1 varies with age [see Equation (2)]	4028.3	$P < 0.05$ *vs.* model 4
6	Model 5 plus Cl varies with albumin	4028.3	Not significant
7	Model 5 plus $Cl_{anhepatic}$ differs from $Cl_{paleohepatic}$	4028.1	Not significant
8	Model 5 plus $V1_{anhepatic}$ differs from $V_{1paleohepatic}$	4028.2	Not significant
9	Model 7 plus $Cl_{paleohepatic}$ differs as a function of venovenous bypass	4028.1	Not significant

Only those models discussed in the text are presented.

* Model 2 and model 4 have the same number of parameters as models 1 and 3, respectively, preventing a formal test of statistical significance. However, the objective function of the former models is markedly improved compared with the latter, indicating that pharmacokinetic parameters should be weight-adjusted.

permitting Cl during the anhepatic period to differ between patients with and without venovenous bypass (model 9). There was no relationship between $Cl_{paleohepatic/anhepatic}$ and blood loss during either of these periods.

Pharmacokinetics of both doses of rocuronium

The previous model (three-compartments with the typical value of V_1 varying with age and the typical value of Cl being the same during the paleohepatic and anhepatic periods) was then applied to the Cp data from both rocuronium doses. In the first analysis, the typical value of Cl did not change during the paleohepatic, anhepatic, and neohepatic periods (table 4, model 10). A second analysis (model 11) permitted the typical value of Cl to change acutely at the beginning of the neohepatic period, but the distribution of Cl values was the same as in the earlier periods (*i.e.*, Cl for each subject was the same fraction of the typical value during each of the periods); this improved the quality of the fit. A model (12) in which the typical value of Cl was the same throughout all periods but the distribution of Cl values changed acutely at the beginning of the anhepatic period also improved the fit. Permitting the typical value of Cl and its interindividual distribution during the neohepatic period to differ from that during the earlier periods further improved the quality of the fit (model 13). Plots of duration of preser-

Table 4. Pharmacokinetic Analyses Using Data from Both Doses of Rocuronium

Model No.	Issue Tested	Objective Function	Statistical Significance
10	Three compartments; parameters weight-adjusted; V_1 varies with age; Cl and V_1 do not vary between periods	8016.1	—
11	Model 10 plus $Cl_{neohepatic}$ differs from $Cl_{paleohepatic/anhepatic}$; interindividual variability in Cl same during these periods	7996.4	$P < 0.05$ *vs.* model 10
12	Model 10 plus interindividual variability in Cl different during neohepatic, compared with paleohepatic/anhepatic, period	7911.3	$P < 0.05$ *vs.* model 10
13	Model 12 plus typical value of Cl and its interindividual variability different during neohepatic, compared with paleohepatic/anhepatic, period	7903.9	$P < 0.05$ *vs.* model 12
14*	Model 13 plus Cl during neohepatic period varies with duration of warm ischemia [see Equation (3)]	7872.0	$P < 0.05$ *vs.* model 13

Only those models discussed in the text are presented. Various models tested whether Cl changed at the beginning of the neohepatic period; models in which V_1 changed at the beginning of the neohepatic period are not presented. The objective function for model 10 is larger than that for model 5 (table 3) because data from both doses are used in its determination.

* "Optimal" model (see Results).

Table 5. Parameters for the "Optimal" Pharmacokinetic Model (14 in table 4)

	Typical Value	Interindividual Variability* (%)
V_1 (ml/kg)	59.1 − 0.946 · (age − 50)	34.1
V_2 (ml/kg)	54.8	23.4
V_3 (ml/kg)	110	23.4
Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)		
Paleohepatic/anhepatic periods	2.47	15.5
Neohepatic period	2.72 − 0.0125 · (warm ischemia duration‡ − 60)	34.4
$Cl_{distribution}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	4.83	39.5
Cl_{slow} ($ml \cdot kg^{-1} \cdot min^{-1}$)	2.07	39.5†

* Computed as $100\% \cdot \sqrt{\omega_v^2}$ where ω^2 = variance(η); 68% of the population lies within this range of the typical value.

† Interindividual variability in V_3 is modeled as identical to that for V_2; the same applies to Cl_{slow} and $Cl_{distribution}$.

‡ Warm ischemia duration is the duration of the period that the donor liver experiences warm ischemia.

vation time ischemia of the donor liver (total duration and duration of warm ischemia) and demographic information of the liver donor *versus* individual pharmacokinetic parameters suggested that increased duration of warm ischemia (defined as the time that the liver was removed from hypothermic storage and placed on the surgical field until its perfusion) was associated with decreased Cl. This observation was incorporated by modeling Cl during the neohepatic period as:

$$\text{Cl(individual)} = \text{Cl(typical)} \cdot (1 + (\text{WarmIschemiaDuration} - 60) \cdot \text{IschemiaFactor}) \quad (3)$$

where WarmIschemiaDuration is the duration of warm ischemia, 60 min is approximately the average duration of this period, and IschemiaFactor is determined in the analysis. This model (14) fit the data better than a model in which the typical value for Cl during the neohepatic was the same for all subjects. Permitting V_1 to change acutely at initiation of the neohepatic period did not improve the quality of fit of the model to the data further.

Thus, the final ("optimal") model had three compartments (table 5). With the population fit, median percent error was −2.6%, and median absolute percent error was 16.5% (fig. 3A); with the *post hoc* fit, median percent error was −0.8%, and median absolute percent error was 8.4% (fig. 3B). The typical value for V_1 decreased with age and was the same during the three periods of transplantation. The typical value for Cl was the same during the paleohepatic and anhepatic periods. During the neohepatic period, Cl varied with the duration of warm ischemia ($r^2 = 0.26$; $P < 0.025$) but

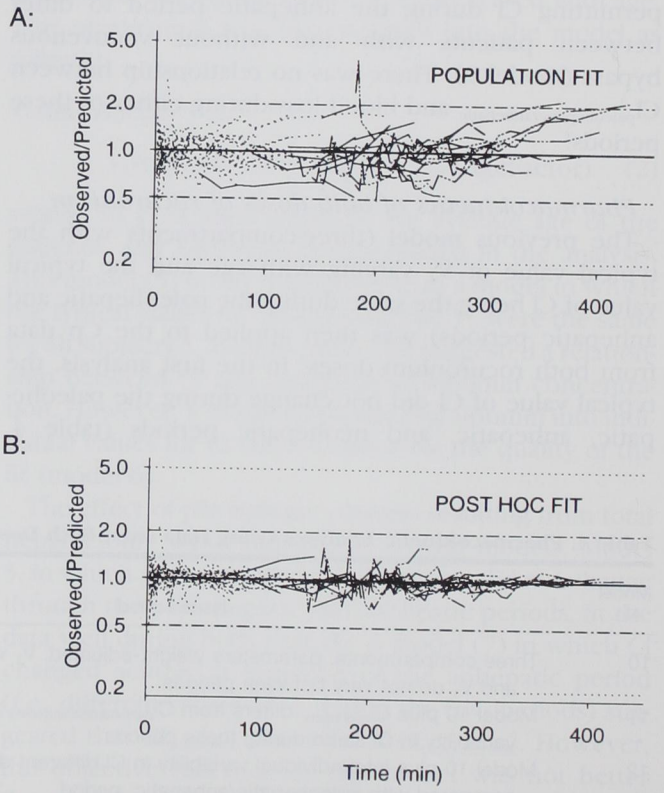

Fig. 3. Relationship between observed plasma rocuronium concentration and that predicted by NONMEM's population analysis (*A*) and NONMEM's *post hoc* step (*B*) with the optimal three-compartment model. The *x* axis is time; the *y* axis is the ratio of observed to predicted concentrations of rocuronium. Each line is from a single individual. *Dotted lines* indicate the paleohepatic period; *solid lines*, the anhepatic period; and *dashed lines*, the neohepatic period. If the observed values were identical to the predicted values, each line would lie horizontally at 1.0.

Table 6. Response to 600 μg/kg Rocuronium (Time to Initial Appearance of Four Components to Train-of-Four Stimulation of the Facial Nerve) in 20 Patients Who Underwent Liver Transplantation, Two of Whom Developed Primary Graft Dysfunction

	Patients without Primary Graft Dysfunction	Patients with Primary Graft Dysfunction
N	18	2
Paleohepatic dose (min)	52 ± 30	75, 30
Neohepatic dose (min)	96 ± 33*	210, 110

Values for patients without primary graft dysfunction are mean ± SD; individual values are shown for patients with primary graft dysfunction.

* Differs from response to paleohepatic dose ($P < 0.05$ by Student's t test for paired data).

not with the total duration of ischemia or weight, height, age, or gender of the donor. For a subject with 60-min warm ischemia, the typical value of Cl during the neohepatic period was slightly (10%) larger than that during the paleohepatic and anhepatic periods. Although the typical value of Cl differed minimally between periods, its interindividual variability was larger during the neohepatic period compared with that during earlier periods (coefficient of variation [the square root of the variance ω^2 of η] was 15.5% during the paleohepatic and anhepatic periods and 34.4% during the neohepatic period).

During the paleohepatic and anhepatic periods, typical values for rapid and slow distribution half-lives and elimination half-life for a 50-yr-old subject with 60-min warm ischemia were 3.2, 17, and 87 min, respectively; during the neohepatic period, these values were 3.1, 17, and 82 min, respectively. Volume of the central compartment and V_{ss} varied with age but did not vary between periods. Typical values of V_1 and V_{ss} for a "typical" 50-yr-old subject were 59 and 224 ml/kg; these values ranged from 69 and 233 ml/kg in the youngest subject (aged 41 yr) to 42 and 207 ml/kg in the oldest subject (aged 68 yr).

Duration of neuromuscular effect

Duration of the second dose of rocuronium was longer than that for the first dose (table 6). Duration of effect of the first dose of rocuronium (during the paleohepatic and anhepatic periods) was not related to individual values of Cl ($r^2 = 0.92$; $P > 0.9$). In contrast, duration of effect of the second dose of rocuronium (during the neohepatic period) correlated with individual values of Cl ($r^2 = 0.48$; $P < 0.001$; fig. 4). The two patients who demonstrated primary graft dysfunction had a duration of effect of the second dose of rocuronium of 210 and 110 min (the former being the longest value in the present study) compared with 96 ± 33 min in the remaining 18 patients. Cl in these two subjects (determined using NONMEM's *post hoc* step) was 1.87 and 1.70 ml/kg, respectively.

Discussion

The profound physiologic changes that occur during liver transplantation would be expected to markedly influence the pharmacokinetics of drugs administered during anesthesia. Yet, we observed relatively few effects of liver transplantation on the pharmacokinetics of rocuronium. One surprising finding is that the typical value of clearance was similar during the paleohepatic and anhepatic periods. Because renal failure does not affect rocuronium's clearance,[4] the liver is likely to be the major route for its elimination. In support of this, two thirds of an administered dose of rocuronium can be recovered from the bile or liver of cats.[5] These findings suggested that the anhepatic period would be associated with a marked decrease in rocuronium's clearance. In contrast, several findings from the present study suggest that rocuronium's clearance is affected minimally by the anhepatic period. First, the Cp *versus* time profile (fig. 1) demonstrates that rocuronium concentrations continue to decrease during the anhepatic period. Second, a model (7) in which clearance was permitted different values during the paleohepatic and

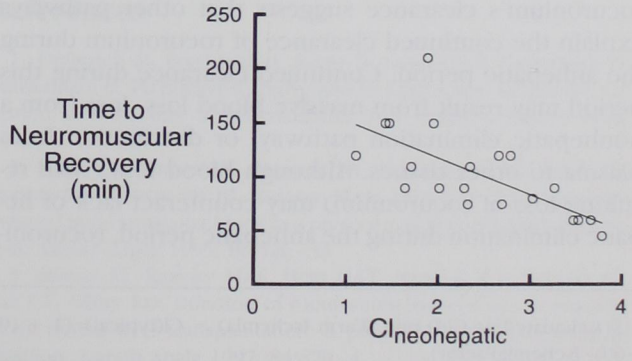

Fig. 4. Values for time to neuromuscular recovery of the second dose of rocuronium are plotted against values for clearance (Cl) during the neohepatic period determined from the "optimal" pharmacokinetic model using NONMEM's *post hoc* step. Time to neuromuscular recovery decreases as Cl increases ($r^2 = 0.48$; $P < 0.001$).

anhepatic periods suggested that clearance decreased only 5% during the latter period; however, this model was not justified statistically compared with a model in which clearance was the same during the two periods. Third, a sensitivity analysis demonstrates that our study design and sampling regimen is adequate to detect a 25% decrease in clearance during the anhepatic period.

Only one study has examined the effect of the anhepatic period on the clearance of a drug eliminated by the liver: Shangraw and Fisher[11] reported that clearance of dichloroacetate (DCA, a compound that limits accumulation of lactate and thereby decreases acidosis during liver transplantation and is believed to be eliminated exclusively by the liver[12]) is absent during the anhepatic period. Several possible explanations could account for these different findings. First, timing of drug dosing differed in the two studies; whereas Shangraw and Fisher gave DCA to some subjects during the anhepatic period, we gave all rocuronium doses during the paleohepatic and neohepatic periods. This resulted in rocuronium concentrations at the time of the anhepatic period typically being less than one tenth of peak values, possibly limiting our ability to detect a small flattening of the plasma concentration *versus* time curve; however, a sensitivity analysis suggests that our study design is sufficient to detect a 25% decrease in clearance during the anhepatic period. Second, rocuronium's pharmacokinetic characteristics (a small V_{ss} and an elimination half-life that is less than the duration of the paleohepatic period) suggest that distribution to peripheral tissue is largely complete before the anhepatic period begins.

If the liver is responsible for most of rocuronium's elimination, the lack of effect of the anhepatic period on rocuronium's clearance suggests that other pathways explain the continued clearance of rocuronium during the anhepatic period. Continued clearance during this period may result from massive blood loss, loss from a nonhepatic elimination pathway, or distribution from plasma to other tissues. Although blood loss (with resulting loss of rocuronium) may counteract lack of hepatic elimination during the anhepatic period, rocuronium's clearance (2.47 $ml \cdot kg^{-1} \cdot min^{-1}$) exceeds blood loss during the anhepatic period (0.11 ± 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$). Loss of rocuronium to the venovenous bypass circuit may be another explanation. However, we used venovenous bypass in only 60% of our patients. In addition, our analyses failed to demonstrate an effect of venovenous bypass on rocuronium's clearance during the anhepatic period. Other physiologic changes during the anhepatic period, such as alterations in cardiac output, changes in circulating blood volume, hypothermia, or acidosis, also may contribute to the continuing decrease of rocuronium concentration during that period. Although we are unable to explain the continued clearance of rocuronium during the anhepatic period, it most likely results from these physiologic events during the anhepatic period of liver transplant surgery.

A second notable finding is that interindividual variability in rocuronium's clearance was larger during the neohepatic period than during the paleohepatic period. One fourth of the variability in clearance during the neohepatic period could be explained by the duration of warm ischemia; the remaining variability in clearance during the neohepatic period could not be explained by variability in the demographics of the donors. The typical practice at Baylor University Medical Center is to remove the liver from cold storage at the beginning of the anhepatic period; therefore, duration of warm ischemia is similar to that of the anhepatic period. Our finding that clearance during the neohepatic period correlates with duration of warm ischemia therefore may result from an effect of the anhepatic period on subsequent clearance *via* either hepatic or renal pathways. However, a more likely explanation is that the liver sustains injury during the period of warm ischemia; our finding supports clinical recommendations to minimize duration of this period.[13]

Our pharmacokinetic model that permitted clearance during the neohepatic period to vary as a function of the duration of warm ischemia suggests that a liver that had no ischemia would result in a clearance of 3.47 $ml \cdot kg^{-1} \cdot min^{-1}$.|||| This value exceeds the typical value for clearance in patients with normal liver function (2.89 $ml \cdot kg^{-1} \cdot min^{-1}$),##[4] and suggests that, except for injury sustained during warm ischemia, the preserved transplanted liver eliminates rocuronium well during the neohepatic period.

Few studies have examined the ability of newly transplanted livers to metabolize anesthetic drugs. Kelley *et al.*[14] studied drug extraction by isolated perfused rat

|||| Calculated as Cl(0 min Warm Ischemia) = Cl(typical) · (1 + (0 −60) · IschemiaFactor).

Although results in patients with normal liver function were not obtained contemporaneously to those in the present study, anesthetic techniques were similar, rocuronium assays were performed in the same laboratory by the same chemist, and the pooled pharmacokinetic analysis was performed by the same investigator.

livers preserved hypothermically for 24 h using a preservation sequence similar to that in the present study (except for an absence of a period of warm ischemia)—preserved livers recovered their ability to extract vecuronium, fentanyl, and morphine to control values within minutes of perfusion. Shangraw and Fisher[11] observed that DCA's clearance was larger during the neohepatic period than during the paleohepatic period, suggesting rapid recovery of function by the transplanted liver. However, they lacked data on DCA's clearance in patients with normal hepatic function; this permitted them to conclude that the transplanted liver functioned better than the native liver but prevented comparisons with the function of normal livers. In addition, Shangraw and Fisher did not examine whether duration of warm ischemia influenced the ability of the transplanted liver to eliminate DCA.

Our third finding is that rocuronium's clearance in the paleohepatic period was 2.45 $ml \cdot kg^{-1} \cdot min^{-1}$, a value slightly less than that observed previously in patients with liver disease undergoing nontransplantation surgery[15] (217 ml/min for patients weighing an average of 76 kg, *i.e.,* approximately 2.85 $ml \cdot kg^{-1} \cdot min^{-1}$) and in healthy control subjects[4] (2.89 $ml \cdot kg^{-1} \cdot min^{-1}$). This suggests that despite sufficient liver disease to necessitate liver transplantation, elimination of rocuronium was compromised minimally in our patients. Similarly, our findings suggest that clearance of rocuronium by the native liver does not predict need for liver transplantation.

Our final finding is that variability in the duration of action of rocuronium (as assessed by time to initial recovery of four components of the train-of-four of the orbicularis oculi muscle) can be explained by variability in rocuronium's clearance. A relationship between individual values of plasma clearance of a muscle relaxant and its duration of action may be expected, but it has rarely been demonstrated. Presumably this occurs because duration of action is a complicated function of several factors (including the small variability of clearance in healthy populations, distribution from central to peripheral compartments producing the initial decrease in plasma concentration, and variability in neuromuscular junction sensitivity) in determining duration of action. Marcel *et al.,*[3] who gave rocuronium, 600 $\mu g/kg$, to 57 patients undergoing liver transplantation, observed that prolonged duration of a dose given at the beginning of the neohepatic period was associated with primary graft dysfunction. Based on results of the present study, it is likely that this prolonged effect of rocuronium resulted from a smaller clearance of rocuronium. In turn, a smaller clearance of rocuronium may have been an early marker of hepatic dysfunction eventually leading to primary graft dysfunction. Our findings support the recommendations of Marcel *et al.* that duration of action of a dose of rocuronium given at the beginning of the neohepatic period may be a sensitive and specific early marker of hepatic dysfunction.

In summary, rocuronium's pharmacokinetics vary minimally during the three phases of liver transplantation. Despite the expected contribution of the liver to the elimination of rocuronium, clearance during the anhepatic period does not differ from that during the paleohepatic period. Because rocuronium is presumably eliminated by the liver, its continued clearance when the liver is absent presumably results from the physiologic events of the anhepatic period of transplantation surgery. During the neohepatic period, the typical value for clearance (for a patient with an average duration of warm ischemia) is slightly more, and interindividual variability is more than that during the paleohepatic period. However, clearance during the neohepatic period is influenced by the duration of warm ischemia, suggesting that the period of warm ischemia is associated with impaired liver function. Finally, interindividual variability in rocuronium's clearance during the neohepatic period explains approximately 50% of the variability of its duration of action. This latter finding supports Marcel *et al.*'s recommendations[3] that assessing duration of action of a dose of rocuronium administered at the beginning of the neohepatic period may assist in early diagnosis of primary graft dysfunction.

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