

Pharmacokinetic analysis of rapacuronium and its metabolite during liver transplantation: an assessment of its potential as a pharmacodynamic probe

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The liver extracts aminosteroidal neuromuscular blocking drugs. We hypothesized that the duration of action of these drugs might provide a pharmacodynamic probe for assessing graft function during orthotopic liver transplantation. The pharmacokinetics of rapacuronium and its active metabolite, ORG 9488, were prospectively studied in 11 patients. Rapacuronium (1.5 mg/kg) was administered at induction of anesthesia, 2 minutes after clamping the portal vein, and 5 minutes after reperfusion of the new graft. Blood samples were drawn at intervals, and an independent laboratory analyzed plasma for both rapacuronium and ORG 9488. Rapacuronium's pharmacokinetics were characterized for 3

stages of the transplant using NONMEM software to construct mixed-effects compartmental models. Rapacuronium plasma clearance during the first stage of orthotopic liver transplantation was 7.25 mL/kg/min. Clearance decreased by only 44% during the anhepatic stage, to 3.91 mL/kg/min, and remained decreased after reperfusion. This effect suggests that an alternate clearance pathway exists. The clearance for ORG 9488 was 13.5 mL/kg/min during the paleohepatic and anhepatic stages, but it decreased 83% on reperfusion, suggesting accumulation after reperfusion. This pharmacokinetic analysis suggests that rapacuronium may not be suitable for use as a pharmacodynamic probe.

It has been demonstrated that the aminosteroid neuromuscular blocking agents vecuronium and rocuronium may be used to identify primary graft dysfunction after liver transplantation by assessing their duration of clinical action (1–5). However, the rate of metabolism of these drugs requires a delay of at least 100 minutes before the diagnosis of primary non-function can be assumed likely. Rapacuronium is a short-duration, rapid-onset neuromuscular blocking agent that was gaining popularity as a replacement drug for succinylcholine when it was withdrawn by the manufacturing pharmaceutical company because of side effects related to bronchospasm. Rapacuronium offered a potentially faster indication of graft dysfunction than vecuronium or rocuronium because of its rapid recovery profile. We examined the pharmacokinetics of rapacuronium to determine if there still might be a unique, beneficial role for this agent as an early detector of liver graft function during liver transplantation.

To act as an effective pharmacodynamic probe for determining liver graft function, a drug must be completely extracted by the liver. Some patients with a severely diseased liver still clear rapacuronium at an apparently normal rate (6, 7). Therefore, we examined the pharmacokinetics of rapacuronium during liver transplantation to determine whether the presence of a cirrhotic liver, the absence of a liver, or the implantation of a liver after prolonged hypothermic ischemia and limited warm ischemia would affect the rate of clearance of rapacuronium.

METHODS

The institutional review board of Baylor University Medical Center approved the study protocol. Informed consent was obtained from 11 patients scheduled for orthotopic liver transplantation. Each patient's preoperative clinical status was graded by using the Child-Turcotte-Pugh (CTP) score system (8). Venovenous bypass was used in 10 patients.

Patients were premedicated with 2 to 3 mg midazolam intravenously. Anesthesia was induced with propofol and fentanyl and maintained with isoflurane and supplemental fentanyl. The patients were mechanically ventilated with oxygen and air; arterial blood gases were monitored to maintain normal acid-base balance. Central venous blood samples were analyzed hourly so that electrolyte balance could be maintained. Body temperature was maintained above 35°C by the use of a heated venovenous bypass circuit and other heating devices.

Rapacuronium (1.5 mg/kg) was administered on 3 occasions during orthotopic liver transplantation: at induction of anesthesia, 2 minutes following portal vein clamping, and 5 minutes after reperfusion of the donor graft. If required, additional muscle relaxation was obtained by administration of cisatracurium. Arterial blood samples (5 mL each) were obtained immediately before each dose of rapacuronium; at 2, 5, 10, 25, 50, and 100 minutes following each administration of rapacuronium; and at 2, 4, 6, 12, and 18 hours after the third dose. Blood samples were centrifuged immediately, and the plasma was stored at –20°C until analysis. The samples were analyzed for rapacuronium and its active metabolite, ORG 9488, by an independent laboratory (Covance Laboratories, Madison, Wis) using high-performance liquid chromatography with mass spectrometry detection. Detec-

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tion was by single ion reaction monitoring. The lower limit of quantification for the study was set at 2.00 ng/mL for both rapacuronium and ORG 9488, with a coefficient of variation of 3.9% at a concentration of 100 ng/mL.

Pharmacokinetic/pharmacodynamic analysis

The analysis was carried out in 2 phases with NONMEM version 5 software running on a SUN Ultra Enterprise computer. Phase 1 determined rapacuronium disposition. The model used during this phase was “fixed” and acted as the input to phase 2. Phase 2 determined the disposition of ORG 9488. Both phases employed a model-building approach; improvements in the criteria of goodness of fit, precision of parameters, and visual acceptability were used to determine when additional parameters should be added to the model.

All individuals were fitted simultaneously to the same model (the population model). Interindividual variability was also estimated in this model for some of the pharmacokinetic parameters. For instance, clearance was modeled as $CL = CL(\text{population}) \times (1 + \eta_{CL})$, where CL is clearance for a given individual, $CL(\text{population})$ is the typical value for clearance in the population, and η_{CL} is a normally distributed random variable with a mean of 0 that takes a new value for each individual. Variability for clearance was estimated as the variance of the η values, and in this case the resultant figure was a coefficient of variation.

Generally, a forward model-building approach was taken, and NONMEM’s first-order minimization algorithm was chosen. Additional parameters were accepted only if they significantly improved the fit of the model to the data. We also tested the “first-order conditional estimates” method, which gave a similar fit, probably because of the small degree of interindividual variation. Finally, when the model-building process was complete, we tested whether each parameter of the model independently improved the fit of the model to the data by excluding each from the model and obtaining a new fit. Parameters were accepted only if they decreased the objective function ($-2 \log$ likelihood) by 3.8 (or 6 for 2 parameters). These values are equivalent to $P < 0.05$ when the objective function is evaluated against the X^2 distribution.

In phase 1, mixed-effects population models were fitted to the rapacuronium plasma concentration data from all 3 stages of the operation. We initially fitted 2- and 3-compartment models with weight-related and non-weight-related parameters. Two-compartment parameters included the volume of the central compartment (V1) and volume of the peripheral compartment (V2). The volume of the third (deep) compartment (V3) was included for the 3-compartment model. Models with interindividual variability parameters in differing numbers of structural pharmacokinetic parameters were then tested. Interindividual variation in a pharmacokinetic parameter was modeled only when this improved the fit of the model to the data. We also attempted to partially model parameters as functions of certain observations (covariate effects such as temperature, gender, cold and warm ischemia times). When this basic modeling process was completed, we attempted to fit models with additional parameters that described changes in pharmacokinetic parameters among the 3 stages of the operation. We also tested

Table 1. Mean values for the pharmacokinetic parameters of the final model for rapacuronium

Parameter	Stage of operation		
	Paleohepatic	Anhepatic	Neohepatic
CL (mL/kg/min)	7.25 (CV 23%)	3.91	3.91
Q2 (mL/kg/min)	9.59 (CV 11%)	no change	no change
Q3 (mL/kg/min)	3.32 (CV 11%)*	no change	no change
V1 ([mL/kg] + mL)	120†	no change	138
V2 (mL/kg)	235	200	200
V3 (mL/kg)	973*	no change	no change

*Data from the first dose of rapacuronium were fit without this compartment.

†These data are for a 70-kg patient; for others, V1 is $(66.1 \times \text{wt}) + 3750$ mL.

CL indicates clearance; CV, coefficient of variation; Q, intercompartmental clearance; V, volume of distribution. Where a coefficient of variation is not given, the variability in that pharmacokinetic parameter was not necessary to describe the data.

a parameter that coded for a quantity of rapacuronium to be removed along with the explanted liver.

Next, we used a similar model-building process to determine a model for rapacuronium’s metabolite. We made the following assumptions:

1. The values for the pharmacokinetics of rapacuronium were fixed to the values determined in the analyses described above (i.e., fitting of the model to ORG 9488 concentrations was not permitted to influence the quality of the fit to the rapacuronium values).
2. The conversion of rapacuronium to ORG 9488 occurred in rapacuronium’s central compartment and was unidirectional.
3. ORG 9488 was eliminated unidirectionally from its central compartment.
4. ORG 9488 distributed to only a single compartment or to central and peripheral compartments.
5. The administered drug contained no ORG 9488.

The fraction of the administered dose of rapacuronium that converted to ORG 9488 ($f_{\text{metabolized}}$) is not known. Thus, the quantity of ORG 9488 produced is unknown and, therefore, volume of distribution and clearances for ORG 9488 cannot be estimated. If the fraction of rapacuronium converted to ORG 9488 is constant for volume of distribution and clearances, then their values can be presented as normalized by $f_{\text{metabolized}}$. Here, we estimated the normalized parameters for ORG 9488.

RESULTS

Eleven patients were included in this study. The patient demographics were as follows. CTP scores were between 8 and 12, with diagnoses including autoimmune hepatitis, hepatitis C, hepatitis B, alcoholic cirrhosis, primary biliary cirrhosis, and retransplantation for graft failure. The mean age of patients was 51 ± 8.8 years; mean weight, 84 ± 29 kg; and mean height, 172.7 ± 14.5 cm. The mean duration of surgery was 459 ± 95.5 minutes. During the procedure, no other nondepolarizing relaxants were administered. The mean estimated blood loss was 1777.3 ± 1243.3 mL, and the mean fluid replacement was 8795 ± 6083 mL of crystalloid solution, 4.4 ± 1.8 units of banked erythrocytes, and 5.2 ± 1.9 units of fresh frozen plasma. The mean intraop-

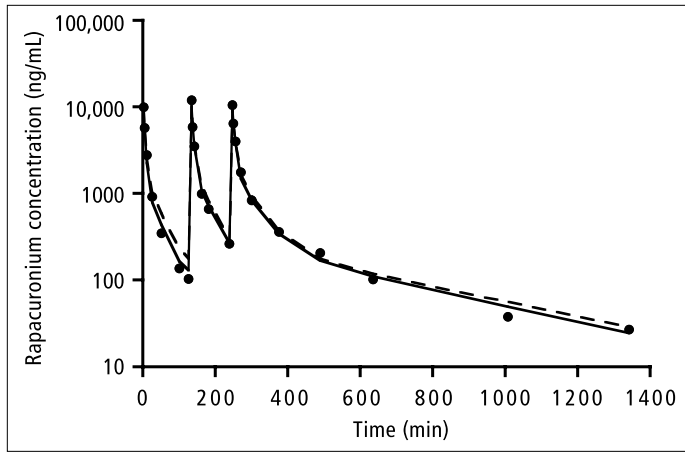


Figure 1. Individual fit, subject 2 (points = observed data; dashed line = prediction based on population model; solid line = prediction based on individualized model).

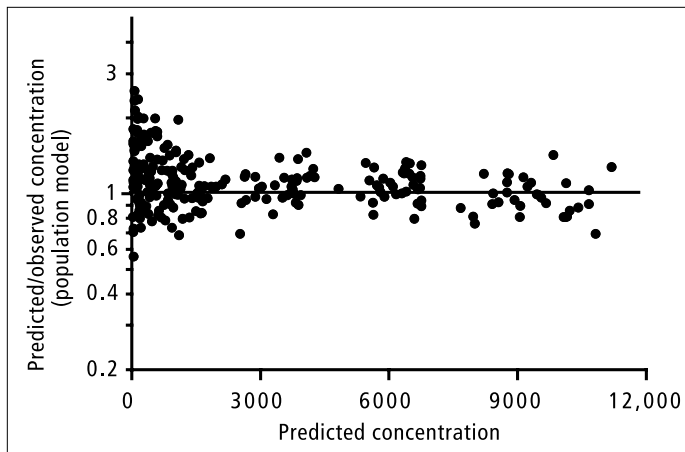


Figure 2. Population predicted values divided by observed values plotted against predicted values.

erative urine output was 1239 ± 929 mL. The warm ischemia time was 65.5 ± 8.0 minutes, and the cold ischemia time was 413.6 ± 151.7 minutes. No episodes of primary graft nonfunction or early dysfunction occurred, as measured by bile production, enzyme assays, and synthetic function.

Pharmacokinetics

A 3-compartment model with weight-related parameters fit the rapacuronium plasma concentration data significantly better than a 2-compartment model or models with non-weight-related parameters. Therefore, a 3-compartment model was chosen for further examination. All parameters were proportional to weight, with the exception of the central volume of distribution, which had both constant and weight-proportional components. No other covariate effects were justified. We explored whether a 3-compartment model was necessary to describe the data for all stages of orthotopic liver transplantation. When a model was fit with 2 compartments and a third was introduced only after reperfusion of the graft, the fit was better than with the basic model and was accepted.

We then investigated whether an additional parameter ("removing" a portion of the peripheral compartment with the isolation of the diseased liver) was justified. Mean values for the parameters of the model during the 3 stages of the operation are

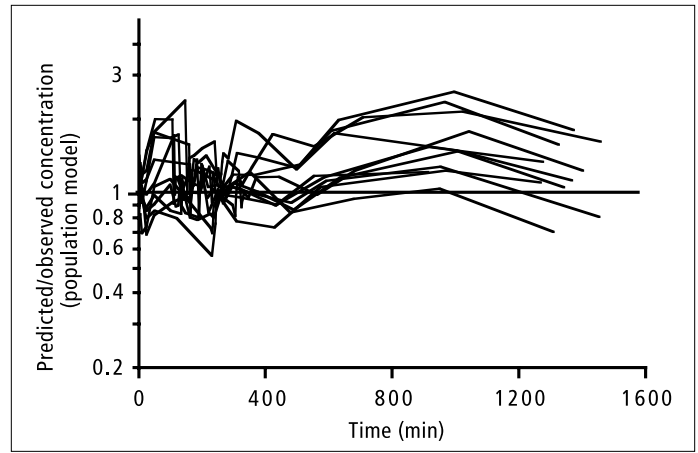


Figure 3. Population predicted values divided by observed values plotted against time. Each line represents 1 subject.

Table 2. Mean values for the pharmacokinetic parameters of the final model for ORG 9488

Parameter	Stage of operation		
	Paleohepatic	Anhepatic	Neohepatic
CL/ <i>f</i> (mL/kg/min)	13.5 (CV 83%)	no change	2.3
Q/ <i>f</i> (mL/kg/min)	315 (CV 29%)	208	no change
V1/ <i>f</i> [(mL/kg) + mL]	same as parent molecule	no change	same as parent molecule
V2/ <i>f</i> (mL/kg)	6668 (CV 25%)	no change	no change

CL indicates clearance; *f*, fraction of rapacuronium that metabolized; Q, inter-compartmental clearance; V, volume of distribution. Where a coefficient of variation is not given, the variability in that pharmacokinetic parameter was not necessary to describe the data.

displayed in *Table 1*. This model fit the data well, and inter-individual variability was small in those pharmacokinetic parameters where it was modeled.

Data from a typical individual are shown in *Figure 1*. The population model predicted individual values well (*Figure 2*). These predictions were only modestly improved with the individual models (*Figure 3*).

A 2-compartment model with parameters proportional to weight fit the metabolite plasma concentration data as well as a 3-compartment model. The 2-compartment model was, therefore, used. The parameters of the final model for ORG 9488 are shown in *Table 2*. Normalized clearance for ORG 9488 remained unchanged with isolation of the liver but decreased substantially with reperfusion of the donor liver.

DISCUSSION

The liver extracts quaternary aminosteroid neuromuscular blocking drugs; therefore, we hypothesized that the duration of action of rapacuronium might offer the clinician a pharmacodynamic probe for liver function during orthotopic liver transplantation. Rapacuronium offered some characteristics that suggest that it would be a more effective pharmacodynamic probe than vecuronium or rocuronium, which have been used previously (1–4). The short duration of pharmacodynamic action of this drug

could potentially give early feedback to the clinician on the status of the liver graft. However, its clearance must be dependent on liver function, and confounding influence from the active metabolite, ORG 9488, should be absent. Therefore, we studied the pharmacokinetics of rapacuronium and ORG 9488 during orthotopic liver transplantation.

The results permit several observations regarding the disposition of rapacuronium. First, the clearance of rapacuronium in this population of patients with severe liver disease was 7.25 mL/kg/min, a value similar to that reported in healthy patients (7). Second, the clearance of rapacuronium in the anhepatic patient was 3.91 mL/kg/min; therefore, elimination of rapacuronium does not cease but declines by only 44% when the diseased liver is isolated from the circulation. Finally, reperfusion of the donor liver did not, within the time limits of this study, restore the clearance of rapacuronium.

The decline in elimination of rapacuronium at liver isolation might be a result of the abrupt curtailment of liver metabolism. An alternative explanation is that major circulatory changes that accompany liver isolation might indirectly result in curtailment of elimination by other routes. For example, reductions in venous return and, consequently, cardiac output that often accompany liver isolation might result in a reduction in renal elimination. Therefore, we cannot conclude from these data that the liver is the only contributor to this component of rapacuronium elimination. Clearance of rapacuronium continued at a rate of 56% of baseline when the liver was excluded from the circulation. This rate might be higher if the major circulatory changes that occur at this time were stabilized. In addition, the failure of the clearance rate to increase with the introduction of the donor liver is a confounding factor that is difficult to explain.

We can also make some observations regarding the disposition of ORG 9488. Normalized clearance (normalized to the fraction of rapacuronium being converted to the metabolite) did not alter with isolation of the diseased liver. This finding may represent a balanced reduction in both the fraction converted and the clearance. Given that ORG 9488 is dependent on renal function for elimination, this altered clearance is consistent with a decline in renal elimination during the anhepatic period. Implantation of the donor liver resulted in a decrease in clearance, possibly reflecting continued problems with renal elimination despite renewed metabolism.

The complex nature of the relative contribution of the liver to aminosteroidal neuromuscular blocking agent elimination has been demonstrated in previous studies (5, 9). Fisher et al showed that the clearance of rocuronium changed insignificantly during the paleohepatic and the anhepatic stages in patients undergoing liver transplantation (6). Studies comparing rocuronium with vecuronium showed that 2 agents are affected differently in liver disease (9, 10). The less potent rocuronium was more dependent on redistribution than on metabolism for termination of action, and it was concluded that the liver does not play a dominant role in the termination of action of rocuronium.

In a clinical study, bolus injections of rapacuronium in patients with cirrhosis (CTP scores of 5–10 [mean 7]) demonstrated that plasma clearance was increased (7). Duration of action of either a single bolus or a 30-minute infusion following a bolus was not clinically affected by liver disease. The residual function

of the liver, even in end-stage disease, may be sufficient to extract rapacuronium.

Differences of clearance between the aminosteroidal muscle relaxants can be explained by the presence of a higher unbound fraction of the newer agents rocuronium and rapacuronium, which leads to shorter equilibration times (11, 12). Rapacuronium has a more rapid redistribution to other tissues than vecuronium or rocuronium, with a greater volume of distribution in diseased livers than in healthy livers (6, 12). Relevant nonenzymatic degradation processes have never been shown for rapacuronium but may be important in clearance times as well.

Rapacuronium was administered at time 0, at portal vein clamping, and at reperfusion. This study design was predisposed to obtain fewer data during the first 2 stages of orthotopic liver transplantation than during the neohepatic stage. The data supported a 3-compartment model, but one of the compartments was very large compared with what we already know about the pharmacokinetics of rapacuronium and other aminosteroidal muscle relaxants. The fit was improved substantially when the parameters of the model were related to weight, with the exception of the initial volume of distribution, which had a constant plus weight-related component. A triexponential equation to fit a pharmacokinetic model was seen early on in pharmacokinetic studies on rapacuronium (11, 12). A 2-compartment model was found to fit during the initial evaluation of rapacuronium and vecuronium (1).

We demonstrated 2 effects with reperfusion of the donor liver. A large third compartment is necessary to explain the data after this point. Aminosteroidal neuromuscular blocking agents usually have a very limited volume of distribution because of their highly polar nature. A third compartment is necessary to describe the data after the third dose, probably because more data are available for a longer time after this dose. Nevertheless, its large size is worthy of comment. We speculate that this is a manifestation of the widespread but minor tissue injury that is known to occur after donor liver reperfusion. The increased central volume of distribution observed may be a manifestation of improved venous return through the liver. The significant blood loss and fluid replacement during these procedures may have played a role in these unexpected results; in 2 earlier studies performed in similar circumstances with different muscle relaxants, however, these factors did not appear to affect the results (2, 3).

The elimination rate of rapacuronium does not appear to recover early after orthotopic liver transplantation, at least not for the duration of our observations, and the clearance of the active metabolite, ORG 9488, is also reduced. Therefore, despite its rapid clearance, rapacuronium does not appear to be a promising pharmacodynamic probe for the early detection of a non-functioning liver graft. This analysis may provide further insight into the future selection of rapidly metabolized neuromuscular blocking agents being considered for use as pharmacodynamic probes.

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