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Pharmacokinetics, Neuromuscular Effects, and Biodisposition of 3-Desacetylvecuronium (Org 7268) in Cats

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The pharmacokinetics, biodisposition, and neuromuscular blocking properties of 3-desacetylvecuronium were studied in 17 adult cats. Animals were divided into three groups: five cats with kidney failure induced by bilateral ligation of the renal pedicles, six cats with galactosamine-induced fulminant hepatitis, and six control cats. An intravenous bolus of 300 $\mu g \cdot kg^{-1}$ of 3-desacetylvecuronium was rapidly injected into the jugular vein. Arterial blood, urine, and bile samples were collected at regular intervals for 6 h in control cats and for 8 h in cats with kidney or liver failure. The liver was excised for analysis at the end of the experiment. In cats with renal failure, 3-desacetylvecuronium pharmacokinetic and pharmacodynamic variables did not differ from those in control cats. In cats with liver failure, plasma clearance was significantly less and mean residence time greater than in control cats (2.8 ± 0.6 *vs.* 14.1 ± 6.5 $ml \cdot kg^{-1} \cdot min^{-1}$ and 334 ± 225 *vs.* 49 ± 29 min, mean ± SD, respectively). Volume of distribution at steady state in cats with liver failure and in control cats was not different. Also, in cats with liver failure, the duration of action and recovery index of 3-desacetylvecuronium was significantly greater than in control cats (168 ± 62 *vs.* 82 ± 32 min, and 39 ± 19 *vs.* 10 ± 4 min, respectively). Onset time of neuromuscular blockade was similar in all three groups. Total recovery of 3-desacetylvecuronium, for all three groups, in urine, bile, and liver was 90 ± 11% (mean ± SD). In control cats, 70 ± 18% of 3-desacetylvecuronium was recovered in bile and liver and 19 ± 14% in urine. No 3,17-bidesacetylvecuronium (a putative 3-desacetylvecuronium metabolite) was detected. In conclusion, 3-desacetylvecuronium is eliminated predominantly by the liver and to a lesser extent by the kidney. Hepatic failure, but not kidney failure, significantly prolonged 3-desacetylvecuronium-induced neuromuscular blockade and mean residence time and significantly decreased plasma clearance. (Key words: Kidney: drug elimination. Liver: fulminant hepatitis; drug elimination. Neuromuscular relaxant: 3-desacetylvecuronium. Pharmacokinetics: 3-desacetylvecuronium.)

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VECURONIUM is a nondepolarizing neuromuscular blocking agent that is used commonly in critical care medicine to facilitate mechanical ventilation. However, there are cases of persistent neuromuscular blockade lasting many hours after discontinuation of long-term administration of vecuronium in critically ill patients.[1] Persistent high plasma concentrations of 3-desacetylvecuronium, the principal metabolite of vecuronium, were found in these patients with prolonged neuromuscular blockade.[1] Because in cats, 3-desacetylvecuronium is at least 50% as potent as vecuronium as a neuromuscular blocking drug,[2,3] these persistent high concentrations of this metabolite have led us to consider whether it is the cause of the prolonged blockade.

The pharmacokinetics of 3-desacetylvecuronium are not known. Two critically ill patients who remained paralyzed after termination of vecuronium administration and in whom high plasma concentrations of 3-desacetylvecuronium were observed had renal failure requiring hemodialysis but not liver failure.[1] Preliminary data obtained in our intensive care unit (ICU) indicate that only patients with decreased renal function have delayed recovery from neuromuscular blockade after discontinuation of long-term administration of vecuronium.[4] However, Bencini *et al.*[3] found that liver clearance is as important for the elimination of 3-desacetylvecuronium as it is for the elimination of parent-compound vecuronium.

We hypothesized that 3-desacetylvecuronium depends primarily on the kidney for its elimination. Therefore, in critical care patients having impaired renal function, elimination of 3-desacetylvecuronium is delayed and neuromuscular blockade persists. To test this hypothesis, we investigated the pharmacokinetics, biodisposition, and neuromuscular blocking properties of 3-desacetylvecuronium in three different groups of cats; one group with kidney failure induced by bilateral ligation of renal pedicles, a second group of cats with galactosamine-induced liver failure, and a third group of control cats having neither of these procedures.

Materials and Methods

With the approval of the University of California Committee on Animal Research, we studied 17 adult cats of either gender weighing 2.6–5.0 kg. The 17 cats were di-

vided into three groups. In the first group (five cats), kidney failure was induced by ligation of both renal pedicles. The second group (six cats) had liver failure resulting from galactosamine-induced fulminant hepatitis. Galactosamine hydrochloride (4.25 mmol · kg^{-1} dissolved in 5% dextrose) was administered intravenously 16 h before injection of 3-desacetylvecuronium.[5] In this group, we measured plasma creatinine concentrations, prothrombin time, serum glutamic oxaloacetic transaminase (SGOT) levels, and total bilirubin plasma concentrations before galactosamine administration (baseline level) and immediately before and 4 h after injection of 3-desacetylvecuronium (*i.e.*, 16 h and 20 h after galactosamine injection). The third group comprised six control cats who received anesthesia and a laparotomy but in whom neither renal nor liver failure was induced.

After preoperative sedation with 9–23 mg · kg^{-1} of ketamine subcutaneously, anesthesia was induced by intravenous injection of 8-28 mg · kg^{-1} of sodium pentobarbital and was maintained with additional intravenous bolus doses of pentobarbital as needed to abolish cardiovascular reflexes to pain and respiratory stimuli. After induction of anesthesia, a tracheostomy was performed and ventilation controlled by a Harvard respirator with room air (tidal volume 10 ml · kg^{-1} and rate 20–30 cycles · min^{-1}). Respiratory rate was altered to maintain carbon dioxide tension (Pa_{CO_2}) at 38–40 mmHg. Arterial blood gases, sampled from the carotid artery, were measured regularly throughout the study to maintain normal values. Arterial blood pressure was monitored *via* a pressure transducer connected to a polyethylene cannula inserted into the carotid artery. Mean arterial pressure was calculated by adding to the diastolic pressure one third of the difference between systolic and diastolic pressures. The right jugular vein was cannulated and used for injection of drugs and fluid replacement. Lactated Ringer's solution was infused at a rate of 8 ml · kg^{-1} · h^{-1} to maintain intravascular fluid balance. Rectal temperature was continuously monitored and maintained at 37 ± 0.5° C by means of a circulating water blanket.

A laparotomy was performed through a midline incision from the xyphoid process to the pubis symphysis. In 13 cats (all of the control animals and animals with kidney failure and two of six animals with liver failure) the cystic duct was ligated and the common bile duct cannulated for collection of bile samples. Because the first two cats with liver failure produced almost no bile (≤0.5 ml in 8 h), and because bile duct cannulation has an increased risk of bleeding that is aggravated by liver failure-induced coagulopathy, we decided not to collect bile in the remaining four cats with hepatic failure. In 12 cats (control and liver failure cats), the urethra was cannulated to obtain urine samples. In all cats with renal failure, the renal pedicles were ligated to induce total renal vascular exclusion. The laparotomy incision was then closed.

Neuromuscular blockade was quantified by recording the force of contraction (twitch tension) of the indirectly stimulated tibialis anterior muscle. The right sciatic nerve was ligated and stimulated by supramaximal square wave stimuli of 0.2-ms duration at a frequency of 0.1 Hz. The evoked isometric contractions of the right tibialis anterior muscle were recorded on a Grass polygraph *via* a Grass FT force displacement transducer. The degree of neuromuscular blockade was expressed as the percentage of depression of twitch tension relative to the baseline value (*i.e.*, the twitch tension observed immediately before 3-desacetylvecuronium injection). The onset time was defined as the interval between the end of injection and maximum depression of twitch tension; the duration of action, as the interval from injection to recovery of 90% of the baseline twitch tension; and the recovery index, as the interval between recovery from 25 to 75% of the baseline twitch tension.

In two separate cats without laparotomy, we studied the effect of an intravenous injection of 4.25 mmol · kg^{-1} of galactosamine on twitch tension. The intravenous injection of 4.25 mmol · kg^{-1} of galactosamine hydrochloride in these two cats induced a small depression of twitch tension (to 86 and 83% of baseline twitch tension) that was maximal after 1 h. These cats were not used for studying 3-desacetylvecuronium pharmacology.

After these preparations, we allowed at least 30 min to stabilize the experimental conditions. Samples of blood, bile (in cats in which the common bile duct was catheterized), and urine (only in cats without renal pedicle ligation) were collected during this period and used as control samples and for calibration purposes. Mean arterial pressure immediately before the injection of 3-desacetylvecuronium was similar in the three groups of cats (90 ± 40 mmHg in controls, 104 ± 18 mmHg in cats with kidney failure, and 91 ± 37 mmHg in cats with liver failure). 3-Desacetylvecuronium bromide solution was freshly prepared by dissolving lyophilized drug in sterile *p*H 7.4 buffer (0.1 M phosphate). 3-Desacetylvecuronium 300 μg · kg^{-1} (six times the ED_{90} dose; *i.e.*, six times the dose that depresses twitch tension to 10% of control value)[3] was then rapidly injected by intravenous bolus into the jugular vein and flushed in with the infusion fluid.

Arterial blood samples (2.2 ml) were collected from the carotid artery at 2, 5, 7, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420, and 480 min after injection. Samples at 420 and 480 min were drawn only from cats with kidney or liver failure. Blood samples were stored on ice and centrifuged within 20 min of sampling, and each milliliter of plasma was buffered with 1 ml NaH_2PO_4 solution (0.8 M). Urine and bile samples were collected

every 30 min for the first 2 h and every hour thereafter. These samples were mixed with 15 μl H_3PO_4 (1 M) per milliliter of urine and bile, to a final *p*H of 5.0 ± 0.2. At the end of the experiment (6 h for normal cats and 8 h for the other cats), the liver was excised, washed with normal saline, weighed, and homogenized in an 0.8 M NaH_2PO_4 solution to 25% (weight/volume). All samples were stored frozen at −30° C until analysis.

The concentrations of 3-desacetylvecuronium and 3,17-desacetylvecuronium in plasma, urine, and bile samples and liver homogenates were measured by capillary gas chromatography.[6] The coefficient of variation of this assay is approximately 11% down to 14 ng · ml^{-1}, and its limit of detection is 5–10 ng · ml^{-1}. Internal validation studies have shown that galactosamine do not interfere with the gas chromatographic analysis of 3-desacetylvecuronium.

Plasma concentration *versus* time data were analyzed by noncompartmental analysis using the BMDP statistical program.[7] The pharmacokinetic parameters of volume of distribution at steady state, plasma clearance, renal clearance, and mean residence time, were calculated for each cat according to standard formulas.[8]

Creatinine concentrations in cats with liver failure were compared using repeated measures analysis of variance because it proved more sensitive than its nonparametric equivalent (the Friedman test). All other variables were compared using nonparametric tests (the Kruskal-Wallis test and Mann-Whitney U test, with Bonferroni correction, for unpaired data, and the Friedman test for repeated measures). All values are expressed either as the mean ± the standard deviation or as the median. Differences were considered significant at $P < 0.05$.

Results

Total recovery of 3-desacetylvecuronium in urine, bile, and liver at the end of the experiment was 90 ± 11% for the 16 cats in which biodisposition was studied and was similar in every group (table 1). No 3,17-bidesacetylvecuronium (the putative metabolite of 3-desacetylvecuronium) was detected in plasma, urine, bile, or liver.

Recovery of 3-desacetylvecuronium in control cats was 35 ± 7% in liver, 36 ± 17% in bile, and 19 ± 14% in urine. Most of the administered dose in cats with kidney failure was recovered in liver and bile (49 ± 9 and 48 ± 14%, respectively), and in cats with liver failure, in liver and urine (45 ± 17% and 40 ± 24%, respectively). Total recovery of 3-desacetylvecuronium in urine was significantly increased in cats with liver failure, as compared with control cats (40 ± 24 and 19 ± 14%, respectively). The total amount of 3-desacetylvecuronium eliminated in bile and urine within 6 h after its administration did not differ significantly in any group (52 ± 9% in control

TABLE 1. Total 3-Desacetylvecuronium Recoveries* in Liver, Bile, and Urine (percent of injected dose)

Cat	Liver	Bile	Urine	Total
Controls				
1	23	46	18	88
2	35	38	4	78
3	42	47	0†	89
4	33	40	22	95
5	41	41	11	93
6	34	2‡	41	77
Mean ± SD	35 ± 7	36 ± 17	19 ± 14	86 ± 7
Renal failure				
1	39	41	—	79
2	61	33	—	93
3	57	41	—	98
4	48	59	—	107
5	53	67	—	110
Mean ± SD	49 ± 9	48 ± 14		97 ± 11
Liver failure				
1	66	0§	25	91
2	50	0§	22	71
3	20	—	80	100
4	39	—	47	85
5	50	—	29	79
Mean ± SD	45 ± 17		40 ± 24¶	88 ± 11

* Total recovery of an iv injection of 300 $\mu g \cdot kg^{-1}$ of 3-desacetylvecuronium in cats (6 h after injection for control cats and 8 h after injection for kidney failure and liver failure cats).

† In control cat 3, no urine was collected despite correct catheterization of the urethra.

‡ Control cat 6 had very low bile flow (0.9 ml for the 6-h experiment *versus* 10.0 ± 1.7 ml for the remaining control cats).

§ Bile collection was obtained from only two of the five liver-failure cats; in those cats no 3-desacetylvecuronium was found (*i.e.*, 0%).

¶ $P < 0.05$ *versus* control.

cats, 46 ± 14% in cats with kidney failure, 38 ± 24% in cats with liver failure).

The pharmacokinetic and pharmacodynamic variables of 3-desacetylvecuronium in cats with renal failure did not differ from control values (tables 2 and 3).

In cats with liver failure, plasma clearance decreased and mean residence time increased compared to those parameters in control cats (2.8 ± 0.6 *vs.* 14.1 ± 6.5 $ml \cdot kg^{-1} \cdot min^{-1}$ and 334 ± 225 *vs.* 49 ± 29 min, respectively). Renal clearance was similar in both the liver failure group and the control group (0.8 ± 0.4 and 1.9 ± 1.7 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively). Volume of distribution at steady state did not differ significantly from control (tables 2 and 3). In the cats with liver failure, the duration of action and recovery index of 3-desacetylvecuronium were significantly greater than in the control cats (two and four times greater, respectively). Onset time of neuromuscular blockade did not differ among the three groups of cats.

We administered 3-desacetylvecuronium 16 h after galactosamine injection to ensure that extensive liver failure in a hemodynamically stable animal would persist for the 8 h required for the study. Cats with galactosamine-induced fulminant hepatitis had a significantly increased prothrombin time (50 ± 18 s 16 h after galactosamine administration), signifying a major decrease in liver synthetic function. SGOT also significantly increased, to as much as 50 times control values 16 h after galactosamine administration (2,807 ± 1,818 in liver failure animals *vs.* 56 ± 19 $IU \cdot l^{-1}$ in controls), signifying extensive hepatocellular injury. Although plasma creatinine concentrations were significantly increased 20 h after galactosamine administration (1.3 ± 0.3 in liver failure animals *vs.* 1.2 ± 0.2 $mg \cdot dl^{-1}$ in controls), the magnitude of the increase was negligible (table 4).

One cat died 21 h after galactosamine administration. Since there was no sign of macroscopic bleeding, this death probably is attributable to interindividual variability in the response to galactosamine and may have been due to cerebral edema and/or hemodynamic collapse from terminal liver failure.[5] Data from this cat have been included in the dynamic analysis but excluded from our analysis of kinetics and biodisposition. Because of the coagulation disorders associated with extensive liver failure, one of the six cats with liver failure had severe hemorrhage. This cat survived for the 8-h study period but did not recover a twitch response. Accordingly, we included this animal's data in our analysis of kinetics and biodisposition but not dynamics.

Discussion

Our results indicate that the liver is the primary organ responsible for elimination of 3-desacetylvecuronium. Only liver failure significantly prolonged the neuromuscular blocking effects and mean residence time of 3-desacetylvecuronium and significantly reduced its plasma clearance; kidney failure modified neither the pharmacokinetics nor the pharmacodynamics of this compound.

TABLE 2. Neuromuscular Blocking Effects* of 3-Desacetylvecuronium

	Cat	Control (n = 6)	Kidney Failure (n = 5)	Liver Failure (n = 5)
Onset time (min)	1	0.5	0.5	0.6
	2	0.7	0.4	0.4
	3	0.4	0.4	0.6
	4	0.5	0.4	0.3
	5	0.7	0.5	0.4
	6	0.6		
Mean ± SD		0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
Duration of action (min)	1	83	71	165
	2	37	35	113
	3	104	103	105
	4	69	31	209
	5	70	25	250
	6	132		
Mean ± SD		82 ± 32	53 ± 33	168 ± 62†
Recovery index (min)	1	4	5	39
	2	6	9	25
	3	17	22	26
	4	12	6	33
	5	13	3	72
	6	11		
Mean ± SD		10 ± 4	9 ± 8	39 ± 19†

* Neuromuscular blocking effects of 300 μg/kg, six times the ED_{90} dose.

† Values are considered different from control values when $P < 0.05$.

TABLE 3. Pharmacokinetic Variables of 3-Desacetylvecuronium

	Cat	Control (n = 6)	Kidney Failure (n = 5)	Liver Failure (n = 5)
Plasma clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	1	8.6	9.4	2.2
	2	17.5	42.7	2.2
	3	12.2	12.0	3.2
	4	23.6	24.5	2.7
	5	16.9	20.4	3.5
	6	5.9		
Mean ± SD		14.1 ± 6.5	21.8 ± 13.2	2.8 ± 0.6*
Renal clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	1	1.6	—	1.1
	2	0.8	—	0.6
	3	0	—	0.3
	4	5.0	—	1.2
	5	1.8	—	1.0
	6	2.3		
Mean ± SD		1.9 ± 1.7	0	0.8 ± 0.4
V_{ss} ($l \cdot kg^{-1}$)	1	0.41	0.67	1.60
	2	0.37	1.89	0.72
	3	0.90	0.79	0.38
	4	0.57	1.40	0.69
	5	0.59	0.17	0.87
	6	0.55		
Mean ± SD		0.56 ± 0.19	0.98 ± 0.67	0.85 ± 0.45
MRT (min)	1	47	72	712
	2	21	44	332
	3	74	66	119
	4	24	57	258
	5	35	8	248
	6	93	—	
Mean ± SD		49 ± 29	49 ± 25	334 ± 225*

* Clearance and mean residence time in cats with liver failure are significantly different from control values ($P < 0.01$).

V_{ss} = apparent volume of distribution at steady state; MRT = mean residence time.

Furthermore, although we were able to nearly completely recover the administered dose of 3-desacetylvecuronium in urine, bile, and liver, the dominant recovery was in bile and liver, further confirming the hepatic pathway as the major route of elimination. 3-desacetylvecuronium does not appear to be metabolized to 3,17-bisdesacetylvecuronium, as none was found in plasma, liver, bile or urine. Thus, our findings do not support the hypothesis that kidney failure reduces elimination of 3-desacetylvecuronium.

Ligation of renal pedicles is a standard animal model in which to assess the effect of the absence of renal function on the pharmacokinetics and pharmacodynamics of a drug. Until recently, no model for hepatic failure suitable for our purposes existed. However, we believe that galactosamine-induced hepatic failure fulfills the necessary criteria for such a model. Galactosamine hydrochloride is a highly selective hepatotoxic carbohydrate[9,10] that has been used widely to produce liver injury in a variety of experimental animals.[5,11] Galactosamine-induced fulminant hepatitis is a model of liver failure that has several advantages.[5] First, galactosamine is a very specific hepatotoxin.[9,10] In contrast, carbon tetrachloride has the disadvantage of possible toxicity to the lung and subsequent

TABLE 4. Liver Function Values Observed during Galactosamine-induced Liver Failure

	Time after Galactosamine Injection (h)		
	0	16*	20
Plasma creatinine ($mg \cdot dl^{-1}$)	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.3†
Prothrombin time‡ (s)	12 ± 1	50 ± 18†	>60†
SGOT§ ($IU \cdot l^{-1}$)	56 ± 19	2807 ± 1818†	4447 ± 905†
Total bilirubin ($mg \cdot dl^{-1}$)	0.2 ± 0.1	0.3 ± 0.2†	0.8 ± 0.4†

Means ± SD.

* 16 h after galactosamine injection corresponds to the time of 3-desacetylvecuronium injection.

† $P < 0.05$ *versus* 0 h (repeated-measures ANOVA).

‡ A prothrombin time > 60 s was considered equal to 60 s for statistical analysis.

§ A serum glutamic oxaloacetic transaminase (SGOT) level > 5000 $UI \cdot l^{-1}$ was considered equal to 5,000 $UI \cdot l^{-1}$ for statistical analysis.

pulmonary edema. Second, the manipulation of galactosamine is not toxic to the investigator. Third, 4.25 $mmol \cdot kg^{-1}$ of galactosamine injected intravenously induces massive liver necrosis within a predictable time. Fourth, galactosamine-induced hepatic injury occurs progressively. Consequently, it does not cause the hemodynamic and metabolic stresses observed with surgical techniques involving the clamping of both hepatic artery and portal vein in animals with a portocaval shunt.[12,13] Because of the stress induced by the acute and prolonged hepatic ischemia and consequent massive necrosis of the liver, such animals usually do not survive long enough to perform long-term studies. Finally, we verified in two cats before starting our study that galactosamine does not markedly influence the neuromuscular response to peripheral nerve stimulation. This verifies the validity of this liver failure model for kinetic and dynamic studies.

Liver failure causes perturbations of the cardiovascular and renal systems. Liver failure decreases mean arterial blood pressure, reduces systemic vascular resistance, and increases or does not affect cardiac index. These changes appear to result from, among other mechanisms, the decreased liver synthesis of plasma renin substrate (angiotensinogen).[11,14] In our study, mean arterial blood pressure did not differ among the groups immediately before injection of 3-desacetylvecuronium. Extensive liver failure also is usually followed by a degree of renal impairment. Blitzer *et al.*[5] observed a slight increase of creatinine plasma concentrations after injection of 4.25 $mmol \cdot l^{-1}$ of galactosamine hydrochloride in rabbits, which became statistically significant 22 h later. We also found a slight, but significant, increase in creatinine plasma concentrations. Unlike other studies using an end-stage liver failure model, any changes in renal and cardiovascular performance in our liver failure animals were minimal. Therefore, we concluded that they had no significant influence on our results.

Our pharmacodynamic results are consistent with those obtained by Bencini *et al.*[3] They also report an increase in the duration of action and the recovery index of 3-desacetylvecuronium during occlusion of hepatic vascular inflow. On the other hand, although they found the same magnitude of increase for duration of action (a two-fold increase), their recovery index (time from 25 to 75% of baseline twitch tension) was increased only 150% during liver exclusion, compared with our 400% increase. This apparent difference may be due to the fact that they administered a lower dose of 3-desacetylvecuronium (one sixth of our dose). With smaller doses, recovery of neuromuscular junction occurs primarily due to drug distribution. However, with large doses, such as those we used, recovery is due predominantly to drug elimination and therefore is prolonged.[15]

Cats with liver failure produced almost no bile; therefore, no 3-desacetylvecuronium was eliminated in bile. In those cats, 3-desacetylvecuronium was removed from plasma by urinary elimination and liver uptake (40 and 45% of the administered dose, respectively). Although a significantly increased urinary elimination of 3-desacetylvecuronium was observed in cats with liver failure, renal clearance remained unchanged as compared to control values (see table 3). The increased urinary elimination of 3-desacetylvecuronium therefore seems to be a consequence of the persistent increase in plasma concentrations resulting from the absence of liver elimination. The finding that the liver contained a similar percentage of the total dose of 3-desacetylvecuronium in the control cats and those with liver failure suggest that liver uptake mechanisms are conserved during galactosamine-induced fulminant hepatitis. Therefore, the liver appears to act as a physiologic storage compartment, able to accumulate 3-desacetylvecuronium even when it is unable to excrete it.

In the control group, the recovery pattern of 3-desacetylvecuronium of two cats differed from that of the other four (see table 1). In control cat 3, despite correct bladder catheterization, no urine was obtained during the 6 h of study; recovery data from this cat are similar to those from the cats with kidney failure (fig. 1). In control cat 6, bile excretion was greatly reduced (0.9 ml for the 6 h of study *vs.* 10.0 ± 1.7 ml for the other control cats). This cat excreted only 2% of the administered dose of 3-desacetylvecuronium in bile, and its recovery pattern was similar to that in the cats with liver failure. In addition, the kinetic values for control cat 6 are closer to those of the cats with liver failure (see fig. 2). This cat probably

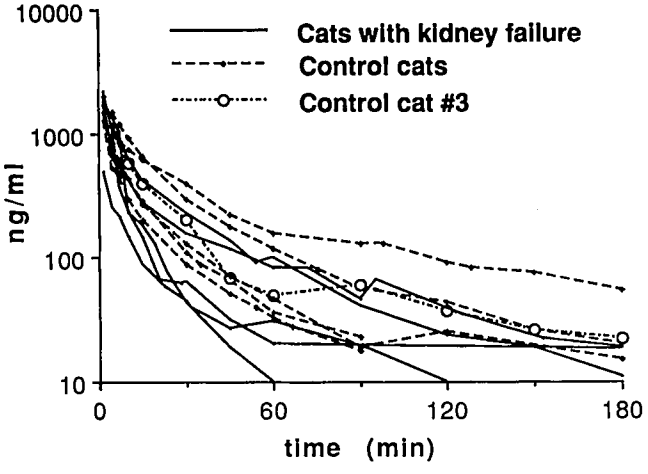

FIG. 1. 3-Desacetylvecuronium plasma concentration *versus* time in cats with kidney failure and control cats. In control cat 3, no urine was collected during the experiment.

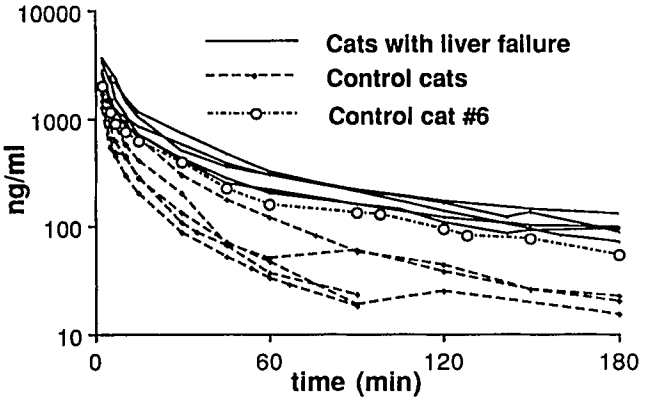

FIG. 2. 3-Desacetylvecuronium plasma concentration *versus* time in cats with liver failure and control cats. Note that the curve of control cat 6, who had very low bile flow during the experiment, is similar to the curves observed in cats with liver failure.

had some hepatic dysfunction, but definite proof is unavailable because we did not test liver function in control cats or in those with renal failure.

We believe that the renal and liver abnormalities found in these two control cats resulted from the trauma caused by the surgery required for our model (laparotomy with cystic duct ligation and bile duct and bladder cannulation). The abnormal behavior of these two control cats, one as having renal impairment and the other as having liver impairment, was completely unexpected; for this reason, we did not think, when designing the study, that measuring renal and liver function was necessary in control cats. All cats used as controls were alert cats that were clinically checked by the veterinarian of the University of California—San Francisco animal care facility. All obtunded animals or animals with abnormal symptoms (*e.g.*, vomiting) also were checked by the veterinarian and were released for experimentation only if the clinical and biologic examinations were satisfactory. The cat in whom no urine was collected had been checked for vomiting a few days earlier and had a normal creatinine plasma level at that time. If the cat in whom no bile was collected had liver impairment, the impairment was not as severe as galactosamine-induced impairment, since the cat was alert and was not vomiting. Therefore, we believe that the abnormal behavior observed in those cats is the result of surgical trauma.

Our results do not help us to explain the accumulation of 3-desacetylvecuronium in patients with kidney failure who have received vecuronium for a prolonged period.[1] In our animal model, decreased plasma clearance and increased mean residence time of the metabolite occurred only in the presence of liver failure. Two hypotheses may explain this apparently contradictory outcome. The first hypothesis is that hepatic uptake and/or excretion mechanisms (as simulated in our study by the liver failure model) may become saturated over long-term administration of vecuronium, leaving only the kidney to eliminate 3-desacetylvecuronium. Should the liver mechanisms of elimination of 3-desacetylvecuronium become saturated in the presence of kidney failure, 3-desacetylvecuronium is likely to accumulate.[16] The second hypothesis is that the 3-desacetylvecuronium excreted in bile may be reabsorbed, creating an enterohepatic cycle.[16] Because in our study design, each cat's common bile duct was cannulated for bile sampling, the proposed enteric absorption of 3-desacetylvecuronium enteric absorption would not have taken place.

This unexpected outcome also may be due to species differences or to limitations in study design. We studied the pharmacology of 3-desacetylvecuronium after a single bolus and not after chronic administration. To determine why 3-desacetylvecuronium accumulates in renal failure patients, we would repeat this study, looking at the effect of renal failure on 3-desacetylvecuronium elimination after long-term administration of vecuronium and 3-desacetylvecuronium, and in this way seek to reveal the intervention of our proposed saturation of hepatic mechanisms.

In summary, because we found that in cats, the liver is the primary organ of 3-desacetylvecuronium elimination, our results do not explain the plasma accumulation of 3-desacetylvecuronium in patients with renal failure. 3-Desacetylvecuronium is eliminated in cats by both the liver and the kidney. Only liver failure significantly prolonged 3-desacetylvecuronium's neuromuscular blocking effects and mean residence time and decreased its plasma clearance, whereas kidney failure modified neither pharmacokinetics nor pharmacodynamics. Additionally, plasma elimination of 3-desacetylvecuronium during liver failure relied on both hepatic uptake and urinary elimination. Further studies using a chronic kidney failure model may explain why this vecuronium metabolite seems to accumulate in ICU patients with kidney failure.

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