DOSE REQUIREMENTS AND PLASMA CONCENTRATIONS OF PIPECURONIUM DURING BILATERAL RENAL EXCLUSION AND ORTHOTOPIC LIVER TRANSPLANTATION IN PIGS

J. F. PITTET, E. TASSONYI, C. SCHOPFER, D. R. MOREL, P. LEEMANN, G. MENTHA, C. LE COULTRE, D. A. STEINIG AND A. BENAKIS

SUMMARY

We have studied five pigs undergoing bilateral clamping of the renal pedicles, seven pigs undergoing orthotopic liver transplantation and three control animals without surgery in order to examine the roles of the kidney and liver in the plasma clearance of pipecuronium. An i.v. infusion of pipecuronium was controlled to maintain a constant 90–95% twitch depression throughout the investigation. The right sciatic nerve was stimulated continuously with supramaximal stimuli at 0.1 Hz and the force of the corresponding evoked isometric muscle contraction was recorded continuously. Control pigs needed an infusion rate of pipecuronium 8–10.7 μg kg^{-1} min^{-1}. In the renal group, it was necessary to reduce the infusion rate of pipecuronium by about 25% after clamping both renal vascular pedicles (P < 0.05 compared with controls); in pigs undergoing liver transplantation, it was necessary to reduce the rate by approximately 80% after clamping hepatic vessels (P < 0.05 compared with controls and from the period after clamping of renal vessels). After hepatic recirculation, the infusion rate of pipecuronium was increased progressively to a rate which corresponded to 50% of baseline values (P < 0.05 compared with the anhepatic phase and from controls). Plasma concentrations of pipecuronium were comparable in the three animal groups and did not change significantly during the study. These data suggest that the liver plays a more important role than the kidney in the plasma clearance of pipecuronium in pigs.

KEY WORDS

Neuromuscular relaxants: pipecuronium. Pharmacokinetics: pipecuronium, liver transplantation, renal function.

Pipecuronium bromide is a new long acting nondepolarizing steroidal neuromuscular blocking drug, which has pharmacodynamic and pharmacokinetic profiles similar to those of pancuronium, but without cardiovascular side effects [1–3]. In patients without renal function, plasma clearance of pipecuronium remains at 60% of normal values, suggesting that only 40% of an administered dose is dependent on the kidneys for its elimination [4]. There are no data available on the role of the liver, except for one animal study in rats indicating minimal hepatic elimination [5].

To evaluate the roles of the kidney and the liver on the dose requirement of pipecuronium, we have measured the rate of infusion and the corresponding plasma concentration of pipecuronium necessary to maintain a steady state neuromuscular block before and after ligature of the renal vascular pedicles, and with and without the liver during orthotopic liver transplantation in pigs.

METHODS

Fifteen pigs (*Sus scrofa* domesticus) weighing 22–25 kg were included in the study, after approval of the Ethics Committee on animal research of our institution. Animals were allocated to three groups: group A as control group ($n = 3$), group B undergoing ligature of both renal vascular pedicles ($n = 5$), and group C undergoing ortho-

J. F. PITTET*, M.D., E. TASSONYI, M.D., D. R. MOREL, M.D., P. LEEMANN, M.D. (Department of Anaesthesiology); C. SCHOPFER, PHARM.D., A BENAKIS, PH.D. (Department of Pharmacology); G. MENTHA, M.D., C. LE COULTRE, M.D., D. A. STEINIG, M.D. (Department of Surgery); University Medical Center, CH-1211 Geneva, Switzerland. Accepted for Publication: June 7, 1990.

*Address for correspondence: Department of Anaesthesia, University Hospital of Geneva, 1211 Geneva 4, Switzerland.

topic liver transplantation ($n = 7$). Animals from the control group underwent identical monitoring and anaesthesia, but without surgery.

Procedure

Each animal received azaperone 4 mg kg^{-1}, ketamine 7.5 mg kg^{-1} and fentanyl 2 µg kg^{-1} i.m. 30 min before anaesthesia comprising 2–3 % isoflurane in oxygen. The trachea was intubated without the use of neuromuscular block and anaesthesia was maintained with 0.5 % isoflurane in oxygen and fentanyl 4 µg kg^{-1} h^{-1}. Ventilation was controlled to keep arterial P_{CO_2} at 5.0–5.5 kPa, and body temperature was maintained at 36.0–37.5 °C with thermoblankets. Normal saline was infused i.v. through a jugular vein at 10 ml kg^{-1} h^{-1}. Mean systemic arterial pressure and central venous pressure were measured using a carotid arterial cannula and a central venous catheter, respectively, and calibrated pressure transducers (1290 A Hewlett–Packard) positioned at the mid-axillary line, and were recorded on a chart recorder (Hewlett–Packard, 78172 A). Arterial pH was maintained at 7.35–7.50 (with sodium bicarbonate, if necessary). The right posterior leg of the pig was immobilized and the sciatic nerve was isolated surgically in the popliteal space. Using a nerve stimulator (Laubscher P1 NS-2B), continuous supramaximal stimulation of 0.2 ms duration at 0.1 Hz frequency was applied directly to the nerve branch supplying the tibialis anterior muscle. The corresponding evoked isometric contraction of the tibialis anterior muscle was recorded continuously by a Grass FT-10 force-displacement transducer on a one-channel recorder (Kipp and Zonen BD 8). After stable anaesthesia had been established for at least 30 min, a single i.v. bolus injection of pipecuronium of 150 µg kg^{-1} was administered, followed 5 min later by an i.v. infusion of pipecuronium delivered by an infusion pump (Vickers Medical, Model SP55) and adjusted continuously to maintain a constant 90–95 % twitch depression. The initial bolus dose of pipecuronium ($ED_{95} = 150 \pm 20$ µg kg^{-1}) was determined by a cumulative dose technique in a preliminary study in five pigs. Blood samples for measurement of pipecuronium concentrations were drawn every 15 min, from 30 min after the beginning of pipecuronium infusion to the end of operation.

In animals undergoing bilateral renal exclusion, both renal vascular pedicles were prepared, and after a 60-min period of stabilization during which

neuromuscular function was recorded, the pedicles were ligated and divided. The laparotomy was closed and the animals were studied during the following 120 min. In animals undergoing orthotopic hepatic transplantation with a second donor liver, the surgical procedure consisted of three parts. The first phase corresponded to the preparation of the vessels for insertion of the cavo–porto–jugular bypass and dissection of hepatic ligaments and vessels to allow the hepatectomy. During the anhepatic (second) phase, splanchnic blood was drained into the internal jugular vein using an external active non-occlusive veno–venous bypass (BP 50 Biomedicus, Minnesota, U.S.A.). The bypass had a priming volume of 320 ml, flow rate of 1000 ± 200 ml min^{-1} and ejection pressure of 100–120 mm Hg. The third phase consisted of the period after recirculation of the graft during which end-to-end anastomosis of the hepatic artery and cholecysto-duodenostomy were performed.

Measurement of plasma concentrations of pipecuronium

One millilitre of whole blood was collected in a heparinized tube and centrifuged immediately at 5000 g for 30 s; 500 µl of plasma was transferred into an Eppendorf tube and frozen quickly to -70 °C in acetone and dry ice. Samples were stored at -70 °C until analysed. Plasma concentrations of pipecuronium were measured by a new technique using iodine-labelled bengal rose [6]. This technique consists of producing a complex between pipecuronium and iodine-labelled bengal rose. By comparison with an appropriate calibration curve, measurement of radioactivity of this complex permits measurement of pipecuronium. The use of ^{125}I-bengal rose with a specific activity of 150 µCi mg^{-1} permitted measurement of pipecuronium to a detection limit of 5 ng ml^{-1}. This assay is linear over the range 5–5000 ng ml^{-1}, with a correlation coefficient of 0.99 in pig plasma. Inter-assay coefficients of correlation (for 10 assays) were 16.1 % at 10 ng ml^{-1} and 5.4 % at 100 ng ml^{-1} of pipecuronium. Intra-assay coefficients of correlation (for 10 assays) were 10.5 % at 10 ng ml^{-1} and 3.2 % at 100 ng ml^{-1} of pipecuronium. Metabolites of pipecuronium and other anaesthetic agents do not interfere with measurement of pipecuronium concentrations [7].

Statistical analysis

In each animal group, recorded variables over

time were compared by one-way analysis of variance for repeated measurements followed by Bonferroni's multiple comparisons test; comparisons between the three animal groups were made using a one-way analysis of variance followed by a Duncan's multiple comparisons test. For all statistical comparisons, differences were considered significant if $P < 0.05$.

RESULTS

Pipecuronium-induced neuromuscular block was stable at 90–95 % twitch depression in each animal of the three groups during the entire investigation. In control animals, a mean infusion rate of pipecuronium of 8.3 µg kg^{-1} min^{-1} (range 8–10.7 µg kg^{-1} min^{-1}) was necessary to maintain neuromuscular block at 90–95 % twitch depression during the 240-min study period (fig. 1). To maintain a similar neuromuscular block in pigs with bilateral renal exclusion, a mean infusion rate of pipecuronium of 8.9 µg kg^{-1} min^{-1} (range 7–11 µg kg^{-1} min^{-1}) was necessary before clamping both renal pedicles (ns at each time interval compared with control animals). After exclusion of both kidneys, the infusion rate had to be reduced significantly within 15 min to mean 6.9 (SEM 0.8) µg kg^{-1} min^{-1} ($P < 0.05$ compared with the period before clamping of renal vessels), and it remained at this lower rate for the 2 h to the end of the study. To maintain block at 90–95 % twitch depression in pigs undergoing liver transplan-
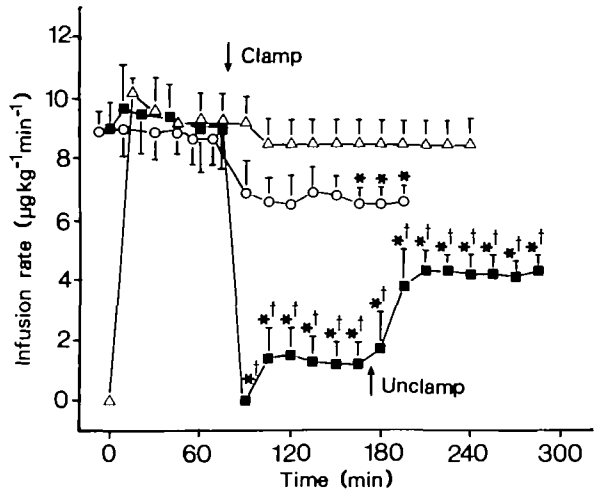

FIG. 1. Mean infusion rate of pipecuronium adjusted to maintain a stable 90–95 % twitch depression in three control pigs (△), in seven pigs undergoing orthotopic liver transplantation (■), and in five pigs undergoing bilateral renal exclusion (○). Data points represent mean (SEM) of values measured every 15 min. Clamp = clamping of renal and hepatic vessels; Unclamp = restoration of hepatic circulation. $P < 0.05$: *compared with control; †compared with pigs with bilateral renal exclusion.

tation, the mean infusion rate of pipecuronium was 9.3 µg kg^{-1} min^{-1} (range 6–12 µg kg^{-1} min^{-1}) during the period before clamping of hepatic vessels (ns at each interval time compared with control animals). After clamping of liver vessels, we observed a rapid increase in the neuromuscular
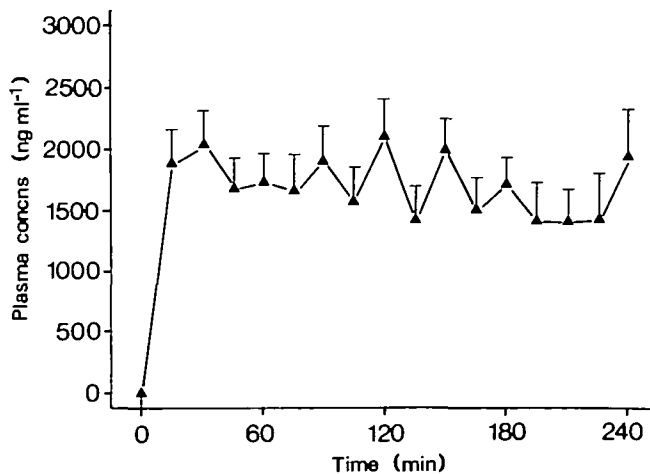

FIG. 2. Plasma concentrations of pipecuronium during a 240-min i.v. infusion of pipecuronium adjusted to maintain a stable 90–95 % twitch depression in control pigs. Data points represent mean (SEM) of three animals measured every 15 min.

block (up to 100%), despite reduction in the
infusion rate. In order to restore 90–95% neuro-
muscular block rapidly, we stopped the infusion
for a short time (10–15 min) and subsequently the
infusion rate of pipecuronium was maintained at
1.2 (0.5) and 1.5 (0.7) μg kg^{-1} min^{-1} up to
recirculation of the liver ($P < 0.05$ for each data
point compared with the period before clamping
of hepatic vessels, controls and the period after
clamping of renal vessels) (fig. 1). To maintain a
comparable neuromuscular block after restoration
of the circulation to the liver, the mean infusion
rate of pipecuronium was increased progressively
over 45 min to 4.3 (0.4) μg kg^{-1} min^{-1} and main-
tained at these values during 60 min up to the
end of the study. These infusion rates were
significantly ($P < 0.05$) greater than those during
the anhepatic phase, but significantly ($P < 0.05$)
less than those during the period before exclusion
of the liver.

Plasma concentrations of pipecuronium in the
control group remained between 1416 (365) ng
ml^{-1} (smallest) and 2098 (299) ng ml^{-1} (greatest)
with a mean value of 1783 ng ml^{-1} and did not
change significantly during the 240-min study
period (fig. 2).

Before and after bilateral renal exclusion,
plasma concentrations of pipecuronium remained
between 1241 (105) ng ml^{-1} (smallest) and 1677
(212) ng ml^{-1} (greatest) with a mean value of 1460
ng ml^{-1} (ns compared with control group) and did
not change significantly during the entire investi-
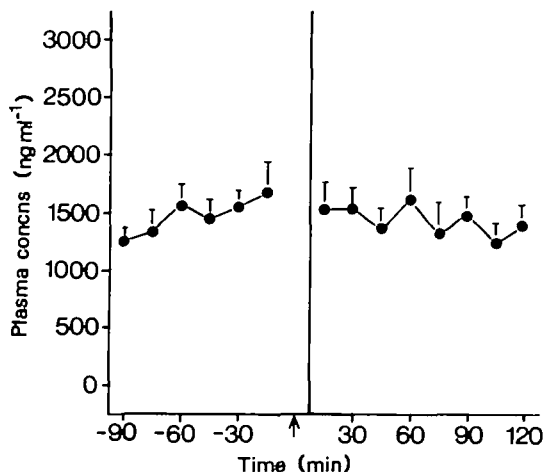gation, despite a 120-min duration of bilateral
renal exclusion (fig. 3).

FIG. 3. Plasma concentrations of pipecuronium before and
after bilateral renal exclusion (↑) in pigs receiving an i.v. in-
fusion of pipecuronium adjusted to maintain a stable 90–95%
twitch depression. Data points represent mean (SEM) of five
animals measured every 15 min, and were not statistically
different over time (two-way ANOVA).

Plasma concentrations of pipecuronium during
the three different phases of liver transplantation
remained between 1332 (257) ng ml^{-1} (lowest) and
2513 (620) ng ml^{-1} (greatest) with a mean value of
1988 ng ml^{-1} (as compared with control group)
and did not change significantly during the entire
investigation, despite a 90-min duration of liver
exclusion (fig. 4).

Rectal temperature was maintained in the
control group at 38.0 ± 0.1 °C, during the three
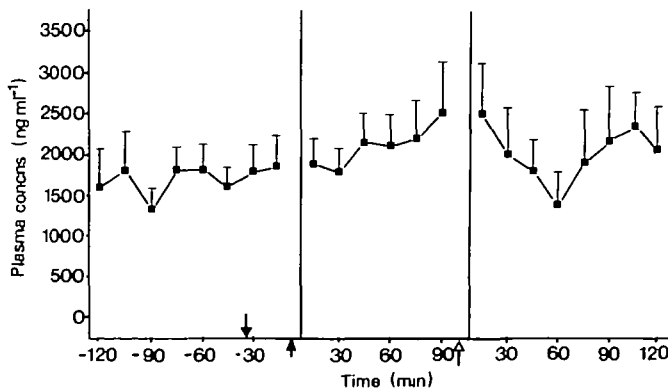phases of liver transplantation (before liver ex-

FIG. 4. Plasma concentrations of pipecuronium during the three phases of orthotopic liver transplantation
in pigs receiving an i.v. infusion of pipecuronium adjusted to maintain a stable 90–95% twitch
depression. ↓ = Crossclamp of hepatic artery; ↑ = crossclamp of portal vein; ⇑ restoration of hepatic
circulation. Data points represent mean (SEM) of seven animals measured every 15 min, and were not
statistically different over time (two-way ANOVA).

TABLE I. *Time course, haemodynamic variables,* Pa_{CO_2}*, arterial pH, and rectal temperature (mean (SEM)) in the three groups of animals. MAP = Mean arterial pressure; CVP = central venous pressure. P < 0.05: *compared with before crossclamping of liver vessels; †between control group and the period before crossclamping of liver vessels*

		Liver transplantation			Renal exclusion	
	Control	Before clamping liver vessels	Anhepatic phase	After hepatic recirculation	Before clamping renal vessels	After clamping renal vessels
Duration (min)	240	128 (7)	95 (5)	122 (10)	90	120
Heart rate (beat min⁻¹)	118 (6)	112 (5)	113 (5)	151 (5)*	115 (6)	113 (7)
MAP (mm Hg)	69 (2)†	92 (3)	78 (3)	88 (3)	74 (6)	72 (5)
CVP (mm Hg)	2 (1)	2 (1)	2 (1)	3 (1)	3 (1)	3 (1)
Pa_{CO_2} (kPa)	4.7 (0.13)	4.5 (0.13)	4.7 (0.13)	4.8 (0.13)	4.8 (0.13)	4.7 (0.13)
Arterial pH	7.41 (0.01)	7.43 (0.01)	7.38 (0.01)*	7.35 (0.01)*	7.43 (0.01)	7.41 (0.01)
Rectal temperature (°C)	38.0 (0.1)	37.8 (0.1)	37.9 (0.1)	37.6 (0.1)	37.9 (0.1)	37.8 (0.1)

clusion: 37.8±0.1 °C; during cross-clamping: 37.9±0.1 °C; after liver recirculation: 37.6 ±0.1 °C) and in animals undergoing bilateral clamping of renal vessels (before kidney exclusion: 37.9±0.1%, after kidney exclusion: 37.8±0.1 °C). Arterial pH remained stable in control animals (7.41 ±0.01) and in animals with bilateral renal exclusion (before kidney exclusion: 7.43±0.01; after kidney exclusion: 7.41±0.01) during the entire study period. In animals undergoing liver transplantation, arterial pH decreased significantly (P < 0.05) during the anhepatic phase compared with the period before clamping of hepatic vessels (7.43±0.01 vs 7.38±0.01, respectively) and remained at values less than control after restoration of the hepatic circulation (7.35 ±0.02).

In the control group and in animals with bilateral renal exclusion, the cardiovascular variables remained within 20 % of baseline during the entire investigation (table I). In animals undergoing liver transplantation, mean systemic arterial pressure and central venous pressure did not change significantly during the three phases of liver transplantation. In contrast, these animals developed significant tachycardia after restoration of hepatic circulation (from 112±5 to 151±5 beat min⁻¹) (P < 0.05).

DISCUSSION

The results of the present study demonstrate that in pigs, bilateral renal exclusion and absence of the liver produced respectively 25 % and 80 % decreases in the dose requirement of pipecuronium necessary to maintain constant neuromuscular block without significant change in plasma concentrations of pipecuronium. This

indicates that the liver plays a more important role than the kidney in plasma clearance of this agent in pigs.

To determine plasma concentrations of pipecuronium, we used a new method based on the production of a complex between pipecuronium and iodine-labelled bengal rose [6]. This assay is specific for the parent compound and does not measure metabolites of pipecuronium. It has detection limits less than those of the colorimetric assay described earlier [7, 8] and gives results comparable to those of the recently published capillary gas chromatographic assay for quaternary ammonium steroidal neuromuscular blocking agents [9].

In control animals, administration of a 150-µg kg⁻¹ bolus and of a 8.3-µg kg⁻¹ min⁻¹ constant rate i.v. infusion of pipecuronium allowed us to produce and maintain a stable 90–95 % twitch depression, which was associated with stable plasma concentrations of pipecuronium during the entire study. Doses of pipecuronium used in this study in pigs were twice the dose necessary in humans [10]. This high requirement for myoneural blockers in pigs has been reported for other drugs, such as atracurium [11], vecuronium and gallamine [12].

To maintain a similar twitch depression in animals undergoing ligature of both renal vascular pedicles, before renal exclusion we needed an infusion rate of pipecuronium comparable to that required in control animals. Plasma concentrations of pipecuronium measured before clamping of renal vessels were also comparable to those determined in the control group. Similarly, infusion rate and plasma concentrations of pipecuronium measured before crossclamping of hepatic vessels were comparable to those measured in

control animals. These findings suggest that our control animals may be considered as true controls, although they did not undergo surgery. Isoflurane anaesthesia (1 MAC) alone does not modify hepatic blood flow [13], and isoflurane in a concentration similar to that used in the present study in association with surgical stress (laparotomy) produces only a small decrease in hepatic blood flow [14].

Exclusion of both kidneys produced a 25% reduction in dose requirement of pipecuronium. Despite significant reduction in infusion rate, plasma concentration of pipecuronium remained stable. Our data are comparable to the 34% reduction in plasma clearance of pipecuronium observed in patients undergoing cadaver renal transplantation [4] compared with clearance in patients with normal renal function. In contrast, in dogs studied 1 h after bilateral renal exclusion, an 85% reduction in plasma clearance of pipecuronium was observed in comparison with control animals [15]. These differences probably reflect species variation.

Exclusion of the liver produced an 80% reduction in dose requirements of pipecuronium necessary to maintain similar neuromuscular block as that before clamping of liver vessels without significant changes in plasma concentrations of this agent. Many factors may explain this change. We did not evaluate renal function of our pigs undergoing liver transplantation but urine output was maintained at values greater than 1 ml $kg^{-1} h^{-1}$ during the entire investigation, and we found a maximal decrease in dose requirements of pipecuronium, after bilateral renal exclusion, of only 25%. Therefore, it is unlikely that changes in renal function alone could explain this decrease in dose requirement. Other important factors affecting pharmacodynamics, such as systemic haemodynamics, temperature or blood pH, remained within the physiological range during the period of liver exclusion. Increased receptor sensitivity and a decrease in volume of distribution of pipecuronium induced by exclusion of the liver could also be evoked. However, during the anhepatic phase, we used an external venovenous bypass to allow drainage of the splanchnic circulation which represents an important part of the total blood volume in pigs, avoiding possible changes in volume of distribution of pipecuronium. In a previous study, we used the same animal model to investigate atracurium, a neuromuscular blocking drug known to be independent

of the kidneys and liver for its elimination [11]. We have found that plasma concentrations and infusion rates of atracurium did not change significantly during the anhepatic phase compared with the period before clamping of the hepatic vessels. In contrast, plasma concentrations of its metabolite laudanosine, known to be metabolized in the liver, increased significantly after exclusion of the liver compared with the period before clamping of the hepatic vessels. Therefore, it is unlikely that increased sensitivity of the neuromuscular junction during the anhepatic phase could explain our findings and we conclude that there is significant hepatic uptake of this neuromuscular blocker in animals with normal liver function. The importance of the liver was further confirmed by the fact that, in all animals, it was necessary to increase the infusion rate of pipecuronium significantly during the first 1 h after reperfusion of the liver graft. However, dose requirement of pipecuronium was significantly less than that before crossclamping of hepatic vessels, probably because of decreased metabolic function of the hepatic graft immediately after transplantation [16]. The reperfusion of the liver graft was followed immediately by a transient decrease in arterial pH, which could also result in a larger dose requirement of pipecuronium. However, the change observed was probably not related to pH, as changes in the dose requirement of pipecuronium occurred after correcting the metabolic acidosis.

In contrast with our findings, Agoston and colleagues reported that, in cats, temporary hepatic exclusion did not alter significantly the intensity and the time-course of the neuromuscular blocking effects of pipecuronium [17]. However, these authors did not measure plasma concentrations of pipecuronium before and during a brief period of portocaval shunting (10 min). It is possible therefore, that changes in the pharmacokinetics of pipecuronium induced by the short exclusion of the liver are not reflected in neuromuscular effects. There may also be species-related differences in hepatic uptake and excretion of pipecuronium, as reported by the same research group for pigs and cats in hepatic uptake of other myoneural blockers [16, 18]. Previous studies have also suggested that there are differences in hepatic uptake and distribution of neuromuscular blocking drugs between the cat and humans [19, 20]. As pig and human liver have similar enzyme systems [21], the pig is probably more rep-

resentative than the cat for studying the influence of the liver on the neuromuscular effects of muscle relaxants.

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