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Pharmacokinetics and Disposition of Pipecuronium Bromide in Dogs with and without Ligated Renal Pedicles

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The pharmacokinetics of pipecuronium bromide have been studied in anesthetized beagle dogs with and without ligated renal pedicles. A gas chromatographic assay was used to measure the plasma, urine, bile concentrations, and liver content of pipecuronium, the later of which was obtained 8 h after injection. Following an iv bolus injection of 0.1 mg/kg, pipecuronium disappeared from the plasma exponentially with distribution half-lives of 3.9 ± 1.1 min and 12.7 ± 9.5 min (mean ± SD), and elimination half-lives of 44.8 ± 2.6 min and 196.7 ± 102.0 min in animals with and without renal pedicle ligation, respectively. Except for the volume of central compartment, all other pharmacokinetic variables differed significantly between the two experimental groups. The elimination half-life was longer (196.7 ± 102 (SD) *vs.* 44.8 ± 2.6 min), plasma clearance slower (5.9 ± 0.8 ml · kg^{-1} · min^{-1} *vs.* 0.9 ± 0.1 ml · kg^{-1} · min^{-1}) and mean residence time longer (221 ± 73 *vs.* 51.1 ± 1.8 min) in dogs with ligated renal pedicles. Eight hours after injection, the recovery of the parent form of pipecuronium approximated 77% of the administered dose in the urine, 4.5% in the bile, and 3.3% in the liver of normal animals. In animals with ligated renal pedicles 16% of the unchanged pipecuronium was excreted into the bile and 10% of the administered dose was recovered from the liver. Since the total recovery of unaltered pipecuronium approximated 85% of the administered dose in the intact animals, biotransformation seems to play an insignificant role in disposition of this new neuromuscular blocking drug. The authors conclude that renal elimination is the primary route by which pipecuronium is cleared from plasma. (Key words: Kidney: transplantation. Neuromuscular relaxants: pipecuronium; pharmacokinetics.)

PIPECURONIUM BROMIDE is a new bisquaternary, nondepolarizing steroidal neuromuscular blocking drug that is long acting with little or no cardiovascular-or histamine-releasing effects[1–3] (fig. 1). Although renal excretion is the most likely route by which pipecuronium is eliminated, this has not been firmly established. In rats, ^{14}C labeled pipecuronium undergoes significant renal excretion.[4,5] Tassonyi *et al.*[6] reported pharmacokinetic studies of pipecuronium in human patients. Unfortunately, they used a relatively insensitive colorimetric assay to measure plasma concentrations; as a result, they could only measure plasma concentrations for 60 min. Caldwell *et al.*[7] found that the duration of neuromuscular blockade was not prolonged in patients with renal failure. However, mean plasma clearance was reduced and mean residence time in the body increased in patients with renal failure.

To clarify the method of elimination, we studied the pharmacokinetics and biodisposition of pipecuronium in dogs. Pharmacokinetic parameters of this drug in plasma and relative roles of renal and hepatic biliary excretion were determined and compared between dogs with and those without renal pedicles. In addition, relative roles of renal and hepatobiliary excretions of pipecuronium were assessed in the normal *versus* renal failure situations.

Materials and Methods

Following approval of the University of California Committee on Animal Research, ten female beagle dogs weighing 16–20 kg were studied. Anesthesia was induced with ketamine, 5 mg/kg sc, followed by 40 mg/kg of sodium pentobarbital iv, and maintained with additional iv bolus doses of pentobarbital as needed. The trachea was intubated without the use of muscle relaxants. Ventilation was controlled with room air delivered by a Harvard respirator at a rate of 16 breaths per min and a tidal volume of 20 ml/kg. Respiratory rate was altered to maintain Pa_{CO_2} at 38–40 mmHg. Rectal temperature was monitored and maintained at 36–37° C by means of a heating blanket. Arterial blood pressure was monitored *via* a pressure transducer connected to a cannula inserted into the femoral artery. Venous access was secured in a forelimb for administration of pipecuronium. Lactated Ringer's solution was infused at a rate of 10 ml · kg^{-1} · h^{-1}.

When the dogs had been anesthetized for at least 1 h, a laparotomy was performed through a midline incision, the cystic duct was ligated, and the common bile duct cannulated for collection of bile samples. In six dogs (normal group), the urinary bladder was visualized and the urethra cannulated to obtain urine samples. In the remaining four dogs, the renal pedicles were ligated to study

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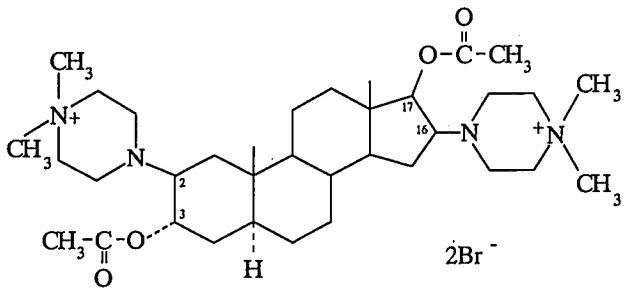

FIG. 1. Structural formula of pipecuronium bromide.

the pharmacokinetics of pipecuronium in the absence of renal elimination. Following this, the laparotomy incision was closed and 30 min were allowed to ensure stabilization of experimental conditions before administration of pipecuronium.

Blank samples of blood (10 ml), urine, (*i.e.*, dogs without renal pedicle ligation only), and bile (10 ml, withdrawn by syringe directly from the gall bladder during the surgical procedure) were obtained and used to determine the calibration curves for pipecuronium. Pipecuronium bromide solution was freshly prepared by dissolving lyophilized drug in sterile normal saline. Pipecuronium 0.1 mg/kg was given as a rapid *iv* bolus and flushed in with infusion fluid.

Arterial blood samples (5 ml) were withdrawn at 2, 5, 7, 10, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, 420, and 480 min after injection. They were stored on ice and centrifuged within 20 min. Each ml of plasma was buffered with 1 ml of sodium dihydrogen phosphate (1 M). Bile and urine samples were collected at 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min and mixed with phosphoric acid to a final *p*H of 5 ± 0.2. At the end of the experiment (8 h), the liver was excised, washed, weighed, and homogenized with sodium dihydrogen phosphate (1 M) to a final volume of 1200 ml. A 100-ml portion of the liver homogenate and the plasma, urine, and bile samples were stored at −30° C until analysis. After the excision of the liver, the animals were killed with 300 mg/kg of sodium pentobarbital and 15 mg/kg of atracurium iv.

Plasma (1 ml), bile, and urine (0.05–0.1 ml), each in duplicate, were extracted selectively for the parent drug as iodide ion pairs into dichloromethane phase. After drying the dichloromethane phase, the residue was dissolved in anhydrous acetone and analyzed for pipecuronium by a capillary gas chromatographic assay method developed in this laboratory.[8] The coefficient of variation is 11.0% at 27 ng/ml and sensitivity 2 ng/ml.

Plasma concentration curves were fitted to two and three compartment models using a computer program for multiexponential kinetic equations. The model best describing the plasma decay curves was selected following the criteria of Boxenbaum *et al.*[9] Statistical analysis was performed using Student's *t* test for unpaired data and differences were considered to be significant at $P < 0.05$.

Results

In dogs without ligated renal pedicles, plasma concentrations of pipecuronium could not be detected beyond 3.5 h after its administration. In contrast, in dogs with renal pedicle ligation, plasma concentrations were detectable until the end of the experiment (8 h) and were higher than in those dogs without renal pedicle ligation throughout the elimination phase (fig. 2). A biexponential function appeared to be most appropriate and a two-com-

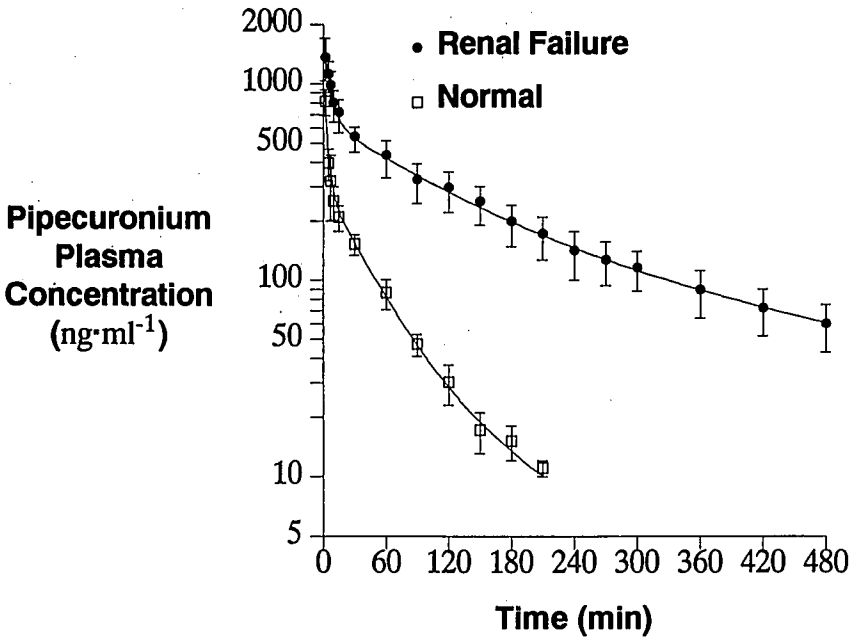

FIG. 2. Semilogarithmic plasma concentration decay curves of pipecuronium (0.1 mg/kg iv bolus) in dogs with (●) and without (□) renal pedicle ligation. Data given as mean ± SD.

TABLE 1. Pharmacokinetic Parameters of Pipecuronium in Dogs

Pharmacokinetic Parameters	Normal	Ligated Renal Pedicles
$T_{1/2}\ \alpha$ (min)*	3.9 ± 1.1	12.7 ± 9.5
$T_{1/2}\ \beta$ (min)*	44.8 ± 2.6	196.7 ± 102
V_{cent} (ml/kg)	111.8 ± 24.5	65 ± 20
Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)*	5.9 ± 0.8	0.9 ± 0.1
$V_{D_{ss}}$ (ml/kg)*	303 ± 51	202 ± 96
M_{RES} (min)*	51.1 ± 1.8	221 ± 73

$T_{1/2}\ \alpha$ = distribution half-life. $T_{1/2}\ \beta$ = elimination half-life. V_{cent} = volume of central compartment. Cl = clearance. $V_{D_{ss}}$ = volume of distribution at steady state. M_{RES} = mean residence time.
* $P < 0.05$.

partment model was therefore selected to calculate the pharmacokinetic variables (table 1). The distribution and elimination half-lives and mean residence times were longer, clearance (CL) slower, and volume of distribution at steady state ($V_{D_{ss}}$) smaller in dogs with renal pedicle ligation (table 1) ($P < 0.05$).

In dogs with intact renal pedicles, 77 ± 5.9% of the injected dose of pipecuronium was eliminated *via* the urine and 4.5 ± 2.2% *via* the bile. An additional 3.3 ± 1.45% was found in the liver 8 h after the administration of pipecuronium (table 2). In dogs with ligated renal pedicles, there was a significant increase in the biliary excretion and liver content of pipecuronium, 16.5 ± 3.8% *vs.* 4.5 ± 2.2% and 10.6 ± 3.9% *vs.* 3.3 ± 1.4% in the dogs with their renal pedicles ligated *versus* those with intact renal pedicles (table 2).

Discussion

The results of this study demonstrate the predominant role of the kidneys in the elimination of pipecuronium in dogs. In animals with ligated renal pedicles, the plasma concentrations of the drug remained significantly higher throughout the elimination phase (fig. 2). In addition, $V_{D_{ss}}$ and Cl were significantly reduced resulting in a fourfold increase in the mean residence time (M_{res}) of pipecuronium in the dogs with ligated renal pedicles (table 1). Development of a capillary gas chromatographic method in this laboratory[8] that is both specific and sensitive for quantitating nanogram levels of pipecuronium has facilitated this investigation.

A major proportion of pipecuronium, approximately 77% of the administered dose, undergoes elimination *via* the kidneys in the unchanged form (table 2). Similar observations have been made in the studies on rats[5] in which urinary excretion accounted for 45% of the administered dose. Pipecuronium seems to be far more dependent on urinary excretion as compared with that of other steroidal neuromuscular blocking drugs. In cats, up to 32% of pancuronium[10] and only 15% of vecuronium[11] could be recovered from the urine during a period of 8 h. The results of this study show that, as in the rat,[5] the biliary elimination of pipecuronium in the dog (4.5%) is considerably less important than that of the other two steroidal muscle relaxants, pancuronium (28%),[10] and vecuronium (40%).[11]

We assume that the preferred mode of renal excretion as compared to biliary route may reflect inherent hydrophilic nature of pipecuronium. In our study, only negligible amounts of pipecuronium (3%) could be recovered from the liver that is far less than the amounts of pancuronium[10] and vecuronium[11] found in the liver in similar experiments.

The fourfold increase of hepatobiliary elimination (table 2) in the absence of renal function in the present study could not compensate for the loss of urinary excretion of pipecuronium. In the dog with and without ligation of renal pedicles, there is a significant difference in total recovery of pipecuronium approximating 27% and 85% of the administered dose, respectively. The possibility that biotransformation of pipecuronium to the potential me-

TABLE 2. Cumulative Urinary and Biliary Excretion and the Liver Content of Pipecuronium after 0.1 mg/kg IV in Dogs with and without Renal Pedicle Ligation

Time after Injection (min)	Normal (n = 6)			With Renal Pedicle Ligation (n = 4)	
	Urine	Bile	Liver	Bile	Liver
0–60	51.1 ± 6.9	1.8 ± 1.3	—	2.1 ± 1.1	—
60–120	64.7 ± 5.2	3.4 ± 2.1	—	6.0 ± 1.8	—
120–180	70.8 ± 4.8	3.9 ± 2.1	—	9.1 ± 2.3*	—
180–240	74.0 ± 5.0	4.2 ± 2.2	—	11.5 ± 2.7*	—
240–300	75.7 ± 5.4	4.4 ± 2.1	—	13.2 ± 3.2*	—
300–360	76.6 ± 5.6	4.4 ± 2.1	—	14.5 ± 3.5*	—
360–420	77.2 ± 5.7	4.4 ± 2.1	—	15.5 ± 3.7*	—
420–480	77.5 ± 5.8	4.5 ± 2.2	3.3 ± 1.4	16.5 ± 3.8*	10.6 ± 3.9*
Total recovery after 8 H		85.2 ± 5.0%		27.1 ± 3.9%	

All values are given as mean ± SD and expressed as percent of the administered dose. Note: there is no urinary excretion in animals with ligated renal pedicles.

* Significantly different from those dogs with intact renal pedicles.

tabolites, 3-desacetyl, 17-desacetyl, and 3-, 17-bisdesacetyl, may occur but can not be excluded especially in the dogs with ligated renal pedicles. That the total recovery of unchanged pipecuronium in animals with intact renal pedicles amounted to 85% of the administered dose precludes any significant amount of biotransformation.

Comparing our results in dogs to those found in humans[7] may lead to the conclusion that humans are less dependent on the kidney for the elimination of pipecuronium than dogs. Clearance was reduced from 2.4 $ml \cdot kg^{-1} \cdot min^{-1}$ in patients with normal renal function to 1.6 $ml \cdot kg^{-1} \cdot min^{-1}$ in patients undergoing kidney transplantation. This 34% reduction in clearance in humans appears to be smaller than the 85% reduction observed in dogs with renal pedicle ligation. There are several factors that could account for the lesser reduction in clearance in humans. First, the transplanted kidney may have excreted some pipecuronium in the later stages of the human study.[7] Thus, the humans may have had limited renal function in contrast to the complete ligation of renal pedicles in dogs. Second, the physiologic responses to chronic renal failure (*e.g.*, increased $V_{D_{ss}}$) in humans may be different than acute ligation of renal pedicles (*e.g.*, decreased $V_{D_{ss}}$) in dogs. Third, the dose of pipecuronium was larger in the dog (*i.e.*, 0.1 mg/kg) as compared to that in humans (*i.e.*, 0.07 mg/kg). Perhaps the larger dose stressed the capacity of the nonrenal excretory mechanisms in dogs. Lastly, there may simply be some species variation. While there are quantitative differences, the overall conclusion that renal excretion remains a dominant route of elimination for both humans and dogs remains.

Based on the above experimental evidence, we conclude that renal excretion is the predominant route of elimination of pipecuronium in the dog. In the absence of renal function the hepatobiliary elimination is increased; however, not sufficiently to compensate for the loss of urinary excretion.

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