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The Influence of Renal Failure on the Pharmacokinetics and Duration of Action of Pipecuronium Bromide in Patients Anesthetized with Halothane and Nitrous Oxide

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The authors determined the pharmacokinetics and duration of action of a bolus dose of pipecuronium bromide (0.07 mg·kg^{-1}) in 40 patients anesthetized with halothane and nitrous oxide. Twenty were patients with normal renal function, undergoing a variety of surgical procedures, and 20 were undergoing cadaver renal transplantation because of end-stage renal disease. Plasma concentrations of pipecuronium were measured for 6 h after administration using a sensitive and specific capillary gas chromatographic assay. Plasma concentration *versus* time data were analyzed by nonlinear regression and fit to a two-compartment or three-compartment model; in addition, the data were analyzed by a non-compartmental method based on statistical moments. Neuromuscular blockade was assessed by measuring the mechanical evoked response of the adductor pollicis muscle to train-of-four stimulation of the ulnar nerve. The pharmacokinetic parameters derived by compartmental modelling were (normal *vs.* renal failure, respectively): volume of distribution at steady state (309 ± 103 *vs.* 442 ± 158 ml·kg^{-1}, mean ± SD), plasma clearance, (2.4 ± 0.6 *vs.* 1.6 ± 0.6 ml·kg^{-1}·min^{-1}), mean residence time (140 ± 63 *vs.* 329 ± 198 min), and elimination half-life (137 ± 68 *vs.* 263 ± 168 min). The same parameters as derived by the non-compartmental method were (normal *vs.* renal failure, respectively): volume of distribution at steady state (307 ± 80 *vs.* 426 ± 119 ml·kg^{-1}, mean ± SD), plasma clearance (2.4 ± 0.6 *vs.* 1.6 ± 0.6 ml·kg^{-1}·min^{-1}), mean residence time (134 ± 41 *vs.* 323 ± 228 min), and elimination half-life (118 ± 35 *vs.* 247 ± 168 min). All these pharmacokinetic parameters differed significantly between the patients with normal renal function and those with renal failure ($P < 0.05$). Despite the pharmacokinetic differences, the mean duration of action (injection to 25% recovery of twitch tension) of pipecuronium was similar in both groups (98 ± 36 min, normal, and 103 ± 60 min, renal failure, mean ± SD). However, the duration of action of pipecuronium in patients with renal failure (range 30–267 min) was more variable than in those with normal renal function (range 55–198 min). This unpredictable response, with the possibility of prolonged blockade, suggests pipecuronium may be less suitable for use in patients with renal failure than the neuromuscular blocking drugs, vecuronium and atracurium, which have a shorter and a more predictable duration of action in these patients. (Key words: Kidney: failure. Neuromuscular relaxants: pipecuronium. Pharmacokinetics: pipecuronium.)

PIPECURONIUM BROMIDE (Arduan®) is a long-acting, nondepolarizing neuromuscular blocking drug. It is similar in structure to pancuronium, but is free of cardiovascular effects.[1] The pharmacokinetics of pipecuronium have been investigated in patients with normal and with impaired renal function[2,3] using a relatively insensitive colorimetric assay to measure the plasma concentrations.[4] Consequently, these were measured for only 60 min after the injection and this short sampling time precluded accurate determination of the elimination phase. However, the results of these studies suggested the plasma clearance of pipecuronium was reduced and its elimination half-life increased in patients with renal impairment. The duration of neuromuscular blockade was not measured in these studies. We have developed a sensitive and specific capillary gas chromatographic assay for the quaternary ammonium steroidal neuromuscular blocking agents that can measure plasma concentrations of pipecuronium for 6 h after administration of usual clinical doses.[5] The aim of our study was to define the pharmacokinetics of pipecuronium in patients with normal or impaired renal function and to determine if the duration of action of the drug was altered in this disease state.

Materials and Methods

With approval from our Committee for Human Research and written informed consent, we studied 20 patients (ASA physical status I or II) with normal renal function, undergoing various surgical procedures, and 20 with

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end-stage renal disease, scheduled for cadaver renal transplantation. Patients were premedicated with diazepam, 10 mg po, or midazolam 0.02–0.05 $mg \cdot kg^{-1}$ iv. Anesthesia was induced with thiopental, 2–6 $mg \cdot kg^{-1}$ iv, and maintained with halothane, 0.7–0.8%, and nitrous oxide, 60–70% (end-tidal concentrations), as determined by mass spectrometry. Esophageal temperature was maintained between 35 and 37° C and ventilation was controlled to maintain the end-tidal P_{CO_2} between 30 and 40 mmHg.

Following induction of anesthesia, subcutaneous needle electrodes were inserted adjacent to the ulnar nerve at the wrist. A Grass® S88 nerve stimulator delivered supramaximal impulses in a train-of-four pattern at 2 Hz at intervals of 15 s. The evoked twitch tension of the adductor pollicis muscle was measured by a Gould Statham® UTC3 force transducer attached to the thumb. Twitch responses were recorded on a polygraph and, following analog-to-digital conversion, on microcomputer floppy disc.¶ When the amplitude of the first twitch response of each train (T1) reached a plateau and stabilized, it was used as the control to which all subsequent T1 responses were compared. The interval between the end of injection of pipecuronium and the return of T1 to 25% of control T1 was recorded as the duration of action.

Pipecuronium, 0.07 $mg \cdot kg^{-1}$, was administered to all patients as a rapid iv bolus. The trachea was intubated following ablation of the twitch response. Venous blood samples were drawn, from a dedicated, peripheral iv cannula, prior to and 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 min after injection. Samples were heparinized, placed on ice, then centrifuged, and the plasma acidified within 1 h. Plasma pipecuronium concentrations (C) were calculated following single organic ion-pair extraction of the drug from the acidified plasma and quantification *via* a sensitive and specific capillary gas chromatographic assay with nitrogen sensitive detection.[5] This assay is specific for pipecuronium and has adequate precision (coefficient of variation 6–11%) over the linear range of 2–5000 $ng \cdot ml^{-1}$.

Concentration *versus* time data were fit to both a two-compartment ($C = Ae^{-\alpha t} + Be^{-\beta t}$) and a three-compartment ($C = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t}$) model by derivative-free, nonlinear regression.[6] All plasma samples were assayed at the same dilution and the variance was approximately in proportion to the concentration; therefore, a weighting factor of $1 \times C^{-2}$ was used. The appropriate model in each case was determined by an F test.[7] The pharmacokinetic parameters of volume of distribution at steady state (Vd_{ss}), plasma clearance (Cl) mean residence time (MRT), and elimination half-life ($t_{1/2}\beta$), were calculated for each patient according to standard formulae.[8,9] For both groups, mean plasma decay curves were constructed by calculating the mean pipecuronium concentration at each time point and fitting these data to a three-compartment model. In addition, because, both two- and three-compartment models were used to fit the data, the pharmacokinetic parameters already described were calculated by a non-compartmental method, based on statistical moments, to confirm the results from the compartmental analysis.[10,11]

Statistical comparisons were made using Student's *t* test for unpaired data. Differences were considered significant at $P < 0.05$.

Results

Mean age and weight for the patients with normal renal function (46 ± 15 yr, 71 ± 13 kg, mean ± SD) did not differ from those with renal failure (44 ± 12 yr and 71 ± 17 kg). Serum albumin and total protein concentrations also were similar for the two groups.

The pharmacokinetic parameters determined for both groups are presented in table 1. A three-compartment model best described the data for 15/20 of the patients with normal renal function and 7/20 of the patients with renal failure. Compared with patients with normal renal function, those with renal failure had a significantly greater Vd_{ss}, a diminished Cl, and a longer MRT and $t_{1/2}\beta$. The values derived by compartmental and non-compartmental methods were similar. In the group with normal renal function the $t_{1/2}\beta$ derived by compartmental modelling appeared slightly greater than that derived by the non-compartmental method (137 *vs.* 118 min). The difference was due almost entirely to the results from two patients in whom the three-compartment model defined a compartment with a small rate constant of elimination at the tail of the pipecuronium plasma concentration decay curve, resulting in large values for $t_{1/2}\beta$ (310 and 342 min). These values for $t_{1/2}\beta$ for these two patients were outliers in this group, but, because the three-compartment model fit the data significantly better than the two-compartment model, the results were retained in the analysis. The values for $t_{1/2}\beta$ derived for these patients by the non-compartmental method (131 and 236 min, respectively) were closer to the mean value for the group.

The transplanted kidneys were *in situ* and producing urine between 1.5 and 3 h after the administration of

¶ Thut PD, Pruzansky E, Rudo FG: Microcomputer use in measuring onset, duration, and recovery from nondepolarizing skeletal muscle relaxants in rabbits. Drug Development Research 5:281–290, 1985.

TABLE 1. Pharmacokinetic Parameters, Derived by Compartmental (Two- or Three-compartment Models), and Non-compartmental (Statistical Moments), Analysis of Pipecuronium Plasma Concentration *Versus* Time Data in Patients with Normal Renal Function or With Renal Failure: Volume of Distribution at Steady State (Vd_{ss}), Plasma Clearance (Cl), Mean Residence Time in the Body (MRT), and Elimination Half-life ($t_{1/2}\beta$). All Values are Mean ± Standard Deviation

		Normal n = 20	Renal Failure n = 20
Vd_{ss} (ml · kg^{-1})*	Compartmental	309 ± 103	442 ± 158
	Non-compartmental	307 ± 80	426 ± 119
Cl (ml · kg^{-1} · min^{-1})*	Compartmental	2.4 ± 0.6	1.6 ± 0.6
	Non-compartmental	2.4 ± 0.6	1.6 ± 0.6
MRT (min)*	Compartmental	140 ± 63	329 ± 198
	Non-compartmental	134 ± 41	323 ± 228
$t_{1/2}\beta$ (min)*	Compartmental	137 ± 68	263 ± 168
	Non-compartmental	118 ± 35	247 ± 168

* $P < 0.05$, normal *versus* renal failure, by both compartmental and non-compartmental methods of analysis.

pipecuronium. We could not identify any specific change in the plasma decay curve of pipecuronium associated with the insertion of the transplanted kidney.

The mean onset and duration of action of pipecuronium in patients with normal and impaired renal function did not differ, but the range of values for the duration of action was greater in the patients with renal failure (table 2). Reversal of neuromuscular blockade, before recovery of T1 to 25% of control, was required for five patients with normal renal function (range 82–130 min) and four patients with renal failure (range 117–173 min). These subjects were not included in the analysis of duration of action.

Discussion

We have used patients undergoing cadaver renal transplantation as our model for renal failure. Similar groups of patients have been used previously to investigate the effect of renal failure on the pharmacokinetics of d-tubocurarine,[12] metocurine,[13] and pancuronium.[14] This group of patients does not represent complete absence of renal function as they receive a cadaver kidney transplant during the study period, and some renal excretion of neuromuscular blocking agent may occur.[12,13] We did not collect urine samples and did not, therefore, quantitate the renal excretion of pipecuronium during the study period. The effect, if any, of renal excretion of pipecuronium would be to diminish differences observed between the patients with normal and impaired renal function. We can conclude, therefore, that the changes we have observed in the Vd_{ss}, Cl, MRT, and $t_{1/2}\beta$, are the least which might be expected if renal function were absent.

The results we obtained may have been influenced by the particular anesthetic technique used. The duration of neuromuscular blockade produced by any nondepolarizing drug will certainly be longer during halothane than during narcotic anesthesia. The influence that the use of a different volatile agent might have had on our results cannot be predicted. The effect of volatile agents on duration of neuromuscular blockade will depend on the volatile agent itself, the concentration of the agent, and the particular neuromuscular blocking drug used.[15] Our conclusions regarding the neuromuscular blockade produced by pipecuronium are, therefore, valid only for the anesthetic conditions described.

The anesthetic technique may also influence the pharmacokinetics of pipecuronium. The principal organs of elimination for the nondepolarizing neuromuscular blocking agents are the kidneys and liver, and different anesthetic agents may have different effects on blood flow through these organs. Although the extraction ratio of the neuromuscular blocking drugs is low, changes in organ perfusion may have some effect on rate of drug elimination.[16] Miller *et al.* found, in the cat, that the elimination half-life of pancuronium, during pentobarbital anesthesia, was shorter than that during halothane, but not enflurane, anesthesia.[17] Results from the cat cannot be extrapolated

TABLE 2. Onset (Time from Injection to Complete Ablation of Twitch Response) and Duration (Time from Injection to Recovery of Twitch Response to 25% of Control) of Neuromuscular Blockade following Pipecuronium 0.07 mg · kg^{-1} iv in Patients with Normal Renal Function and With Renal Failure

	Group	Mean ± SD	Range
Onset (min)	Normal	3.0 ± 0.9	1.5–4.5
	Renal failure	3.6 ± 1.1	2.3–6.5
Duration (min)	Normal	98 ± 36	55–198
	Renal failure	103 ± 60	30–267

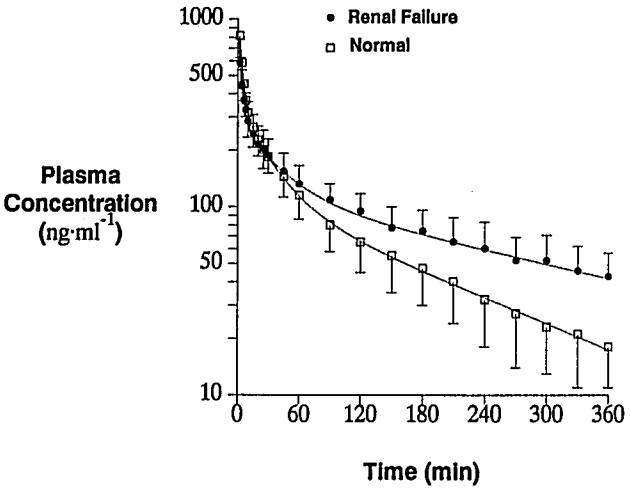

FIG. 1. Mean plasma concentration *versus* time curves for pipecuronium in patients with normal renal function (n = 20) and with renal failure (n = 20). Each point is the mean of all the values at that time point. Error bars are standard deviation. The curves represent the best fit of a three-compartment model to each set of data and are described by the equations $C = 897 \times e^{-0.52t} + 244 \times e^{-0.035t} + 117 \times e^{-0.0055t}$ (normal function) and $C = 509 \times e^{-0.27t} + 177 \times e^{-0.028t} + 118 \times e^{0.-0029t}$ (renal failure), where C is the plasma concentration ($ng \cdot ml^{-1}$) at time t.

directly to the human, but it appears that the anesthetic technique might have some influence on the pharmacokinetics of the neuromuscular blocking drugs. We cannot, therefore, claim that the pharmacokinetic parameters we have derived for pipecuronium will be the same under other anesthetic conditions.

Tassonyi *et al.*, in two separate studies, investigated the pharmacokinetics of pipecuronium in patients with normal and impaired renal function.[2,3] They used a relatively insensitive colorimetric assay and sampled for only 60 min after the injection of pipecuronium.[4] It is likely, therefore, that they underestimated the elimination half-life and overestimated the clearance of pipecuronium. This would explain why the mean values they reported ($t_{1/2}\beta$, 44 min, and Cl, 320 $ml \cdot min^{-1}$) for pipecuronium in patients with normal renal function differ from ours. In addition, all the patients in our group with renal failure had end-stage renal disease, while those in the study of Tassonyi had differing degrees of renal impairment.[3] Although these differences limit the value of direct comparisons, both studies demonstrated that the Cl of pipecuronium is reduced by renal failure. This suggests that renal mechanisms are important in the elimination of this drug.

In our study, Cl was reduced by only 33% in patients with renal failure. There are two reasons why we did not demonstrate a greater reduction in Cl in these patients. First, the transplanted kidney was *in situ* and large volumes of urine were being produced in the latter stages of the study. As has been discussed above, although the excretory function of a transplanted kidney is poor, there may have been some elimination of pipecuronium in the urine during the period of the study. Second, the mean $t_{1/2}\beta$ in the renal failure group was 263 min and the sampling time only 360 min. A longer sampling time may have allowed identification of a slower component to the plasma decay curve, which would reduce the estimate for Cl.

Sampling was limited to 6 h because, after this time, the plasma pipecuronium concentrations in patients with normal renal function fell below a level that we could measure consistently. Although it would have been possible to measure pipecuronium plasma concentrations for a longer period in the patients with renal failure, this was not done, because it would have made direct comparison of the results from the two patient groups difficult due to the influence of the different sampling periods on the pharmacokinetic results.

We have already criticized the results of Tassonyi *et al.* because they sampled for an inadequate length of time. Inspection of the plasma decay curve of pipecuronium (fig. 1) will show that their sampling period (60 min) was during the distribution phase and accurate determination of the elimination phase was not possible. In our study, although the sampling period in the patients with renal failure might be considered short in comparison to the elimination half-life of pipecuronium, we sampled well into the elimination phase and, consequently, errors in our estimates of the pharmacokinetic parameters are likely to be small.

Other possible mechanisms contributing to the clearance of pipecuronium are hepatic elimination and metabolic degradation. In the rat, there is only minimal hepatic elimination of pipecuronium.[18] If this pattern were similar in humans, hepatic mechanisms would not contribute significantly to the Cl. We were unable to quantitate metabolite concentrations in the plasma, urine, and bile, and can, consequently, draw no conclusions about the contribution of metabolic breakdown to the elimination of pipecuronium.

In our study, the Vd_{ss} of pipecuronium was larger in patients with renal failure. This increase in distribution volume may be due to increases in extracellular fluid volumes or to decreased protein binding associated with renal failure.[19] Although all our patients were dialyzed to within 3–4 kg of their estimated dry weight in the 24 h preceeding surgery and none were severely edematous, there may, however, have been alterations in the normal fluid compartments secondary to concomitant pathological

processes, such as diabetes mellitus or cardiovascular disease, both common in this group of patients.

The effect of renal failure on plasma protein binding of pipecuronium has not been investigated. Wood *et al.* found that pancuronium was only 7–11% protein bound in normal subjects and that this was not significantly altered by renal failure,[20] although their patients were not receiving hemodialysis, which is known to affect binding.[21]** Other estimates for the protein binding of pancuronium range up to 87%.[22] However, the experimental conditions of the Wood *et al.* study with respect to the *p*H, temperature, and nature of the medium in which protein binding was measured more closely resembled those observed during clinical practice than the experimental conditions used in other studies. This suggests that the results of the Wood *et al.* study are likely to be an accurate estimate of the protein binding of pancuronium under physiologic conditions.

The patients in our study were receiving multiple drugs, most commonly antihypertensive agents, immunosuppressants, antibiotics, and, often, insulin. Interactions with these agents may have altered the protein binding characteristics of pipecuronium. If pipecuronium protein binding is low, changes in the bound fraction of the drug will have little influence over the concentration of the biologically active unbound fraction. Therefore, altered protein binding remains a possible explanation for the increased Vd_{ss} we observed in the patients with renal failure only if pipecuronium is more highly protein bound than is pancuronium.

Pipecuronium is structurally similar to pancuronium, a drug whose pharmacokinetics have been extensively studied. If the results from our study are compared with the results from previous studies of pancuronium pharmacokinetics, it appears that pipecuronium has a more rapid Cl and perhaps a greater Vd_{ss} than pancuronium.[23]

Although the mean duration of neuromuscular blockade was not longer, it was more variable in the patients with renal failure (table 2); both the shortest (30 min) and longest (267 min) durations of blockade occured in these patients. We found no correlation between any pharmacokinetic parameter and the duration of neuromuscular blockade.

The results for duration of action may have been affected by the need to reverse neuromuscular blockade in some patients before T1 recovered to 25%. However, the times at which this was done and the degree of recovery present at that time was too variable to allow conclusions to be drawn. In this study, the patients received only a single bolus dose of muscle relaxant, and the recovery of twitch tension to 25% of control took a mean time of approximately 100 min. At this time, there was little difference in the plasma concentration of pipecuronium between patients with normal and impaired renal function (fig. 1). However, since recovery from subsequent doses will rely on drug elimination rather than distribution,[24] it is likely the duration of action of such doses will be prolonged in patients with renal failure compared to those with normal renal function. This unpredictable duration of action with the possibility of prolonged blockade places emphasis on the need, in clinical practice, to monitor neuromuscular blockade. This variable response, with the possibility of prolonged blockade, suggests pipecuronium may be less suitable for use in patients with renal failure than vecuronium and atracurium, which have a shorter and more predictable duration of action.

In summary, we used a capillary gas chromatographic assay to determine the pharmacokinetics of pipecuronium bromide in patients with normal and impaired renal function anesthetized with halothane and nitrous oxide. The Vd_{ss} of pipecuronium is greater, the Cl lower, and the duration of action more variable in patients with renal failure, compared to patients with normal renal function.

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