Title: THE INFLUENCE OF RENAL FAILURE ON THE PHARMACOKINETICS AND DURATION OF ACTION OF PIPECURONIUM BROMIDE.

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Introduction. Pipecuronium bromide (ARDUAN) is a synthetic bisquaternary ammonium compound with neuromuscular blocking propeties. It is an analogue of pancuronium and has a similar duration of action but is devoid of cardiovascular side-effects[1]. A study in rats demonstrated that the principal route of elimination of pipecuronium was via the kidneys[2]. The only previous study in humans was limited by the insensitive assay employed[3]. The aim of the present study was to investigate, using a recently developed, sensitive and specific assay, the influence of renal failure on the phamacokinetics and duration of action of pipecuronium bromide.

Methods. The study was approved by our Committee for Human Research. Fifteen patients with normal renal function and 17 with end-stage renal disease, scheduled for cadaver renal transplantation, were studied. Anesthesia was induced with thiopental and maintained with nitrous oxide 60% and halothane 0.7-0.8% (end-tidal concentrations). Esophageal temperature was maintained at 35-37°C and end-tidal CO_2 tension at 30-40 mmHg. Supramaximal stimuli of 0.2 msec duration, in a train-of-four sequence, were applied, via sub-cutaneous needle electrodes, to the ulnar nerve at the wrist. Neuromuscular blockade was assessed by measuring the mechanical evoked response of the adductor pollicis muscle to the first stimulus in each train. When conditions had stabilised, pipecuronium 0.07 mg/kg was injected rapidly i.v. and venous blood was sampled at intervals increasing from 2 to 30 minutes for the next 360 minutes. The times from injection of pipecuronium until the muscle twitch response returned to 5% (DUR5) and 25% (DUR25) of control were recorded.

Following acidification of the samples, plasma concentrations were obtained by organic ion-pair extraction of the drugs and quantification via a capillary gas chromatographic assay with nitrogen sensitive detection. Data were analysed by non-linear regression and described by a two or three compartment model as appropriate for each case. The following parameters were derived:-

Volume of the central compartment - V_{cent}

Volume of distribution at steady state - V_dss

Distribution half life - $t_{1/2}A$

Elimination half life - $t_{1/2}B$

Plasma clearance - Cl

Mean residence time - Mres.

Student's t test for unpaired data was employed for statistical comparison of the groups.

Results. Renal failure was associated with an increase in the steady state volume of distribution, a prolongation of the elimination half life, a reduction in plasma clearance and an increase in the mean residence time. The clinical duration (Dur25) was not prolonged by renal failure but the variability in this parameter was obviously greater. There was no correlation between Dur5 or Dur25 and any pharmacokinetic parameter.
All results are mean ± standard deviation.

Parameter	Normal n = 15	Renal Failure n = 17
V_{cent} (ml/kg)	72 ± 33	104 ± 49
V_dss (ml/kg)*	312 ± 102	448 ± 169
$t_{1/2}A$ (min)	14.8 ± 10.6	16.1 ± 13.4
$t_{1/2}B$ (min)*	127 ± 54	275 ± 179
Cl (ml/kg/min)*	2.5 ± 0.5	1.5 ± 0.5
Mres (min)*	127 ± 44	341 ± 210
Dur5 (min)@	64 ± 25	58 ± 30
Dur25 (min)#	85 ± 19	111 ± 60

* $P < 0.05$, @ n = 13 and 17, # n = 12 and 14 resp.

Discussion. Despite the virtual absence of renal function, clearance remained 60% Of normal, suggesting that only 40% of the injected dose was dependant on the kidney for its elimination. The greater V_dss in renal failure may be due to a an increase in ECF volume or decresed protein binding. These results show that in renal failure there is a significant change in the pharmacokinetic profile of pipecuronium and a greater variability in it's duration of action.

References.

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