Title: PIPECURONIUM AND PANCURONIUM: A COMPARISON OF THEIR PHARMACOKINETICS AND DURATIONS OF ACTION.

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Introduction. Savarese and Kitz in 1975 suggested that there was a need in clinical practice for a neuromuscular blocking agent with a long duration of action and no cardiovascular side-effects[1]. Pipecuronium bromide (ARDUAN), an analogue of pancuronium, fulfils these criteria[2]. A previous study of the pharmacokinetics of this drug was limited by the insensitivity of the assay employed[3]. This problem has been overcome by the development, within our group, of a sensitive and specific gas chromatographic assay. The purpose of the present study was to compare both the pharmacokinetics and duration of action of pipecuronium to those of pancuronium under the same experimental conditions.

Methods. Approval was obtained from our Committee for Human Research and a total of 28 patients were studied. Anesthesia was induced with thiopental 1-4 mg/kg i.v. and maintained with nitrous oxide 60% and halothane 0.7-0.8% (end-tidal) concentrations. Esophageal temperature was maintained at 35-37 ^{o}C and end-tidal CO_2 tension between 30 and 40 mmHg. Supramaximal stimuli of 0.2 msec duration, in a train-of-four sequence (2 Hz), were applied, via subcutaneous 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 were stable, pipecuronium 0.07 mg/kg or pancuronium 0.1 mg/kg was injected rapidly i.v. Venous blood was sampled at intervals increasing from 2 to 30 minutes for the next 360 minutes. The times from injection of the drug 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. Compared with pancuronium, pipecuronium had a more rapid plasma clearance, larger steady state volume of distribution and a shorter Dur25. In all other respects the drugs were similar. All results mean ± standard deviation.

Parameters	Pipecuronium n = 15	Pancuronium n = 13
V_{cent} (ml/kg)	72 ± 33	58 ± 17
V_dss (ml/kg)*	312 ± 102	177 ± 44
$t_{1/2}^A$ (min)	14.8 ± 10.6	13.0 ± 13.3
$t_{1/2}^B$ (min)	127 ± 54	108 ± 33
Cl (ml/kg/min)*	2.5 ± 0.5	1.4 ± 0.3
Mres (min)	127 ± 44	129 ± 29
Dur5 (min)@	64 ± 25	81 ± 24
Dur25 (min)* #	85 ± 19	119 ± 43

* $P < 0.05$, @ n = 13 and 12, # n = 12 and 9 resp.

Discussion. There are significant structural differences between pipecuronium and pancuronium. As a consequence, the two compounds may have different hydrophilic or protein binding properties. This may account for the higher steady state distribution volume and more rapid plasma clearance of pipecuronium. The net effect, however, is that the elimination half lives and mean residence times of both drugs are similar. Interpretation of the durations of action is complicated by the fact that in some cases surgery was completed before the twitch response recovered to 25%. Pipecuronium is clearly a long-acting agent, although, in this study, it's duration of action was shorter than that of pancuronium. Our results suggest that in clinical use the time course of action of the drugs will be similar. Pipecuronium may therefore replace pancuronium in situations where the absence of cardiovascular side-effects is considered advantageous.

References.

1. Savarese JJ, Kitz RJ: Does clinical anaesthesia need new neuromuscular blocking agents. Anesthesiology 42:236-239, 1975

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