

Title : PANCURONIUM : PHARMACOKINETICS AND PHARMACODYNAMICS IN THE ELDERLY.

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Introduction: Previous investigators have shown a decreased plasma clearance of pancuronium according to age (1), suggesting a prolonged duration of the neuromuscular blocking effect of pancuronium in the elderly. The present study was designed to evaluate the effect of aging on both pharmacokinetics and pharmacodynamics of pancuronium and to answer the question whether pancuronium exerts a more pronounced and prolonged effect in the elderly.

Methods: 22 elderly patients ranging in age from 75 to 86 years (mean : 80) were studied and compared to younger patients whose age ranged from 25 to 55 years (mean : 39). Informed consent and approval by Human Studies Committee were obtained. Anesthesia was induced with thiopentone, 4 to 6 mg/kg, and fentanyl, 2.5 to 4 μ g/kg. Tracheal intubation was done after local anesthesia of the larynx with 5% lidocaine. In the first section of the study, the pharmacokinetics of pancuronium were compared between the two groups of patients. A single bolus dose of pancuronium was administered. The dose was established according to the expected duration of operation. Serial blood samples were withdrawn 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300 and 360 min after relaxant administration. Plasma concentrations were measured spectrofluorimetrically (2). The plasma concentration-time data were analysed according to a two-compartment open model. The following pharmacokinetic parameters were calculated : the half-lives of the distribution phase (T 1/2 α) and of the elimination phase (T 1/2 β), the total apparent volume of distribution at a steady state (V_d _{ss}) and the plasma clearance (Cl).

In the second part of the study, the pharmacodynamics of pancuronium were characterized. The force of thumb adduction produced by supramaximal stimulation of the ulnar nerve was recorded. Each patient received a bolus dose of 20 μ g/kg of pancuronium followed by repeated doses of 10 μ g/kg until 95% depression of the twitch height was obtained. The dose of pancuronium which caused a 50% decrease in twitch tension (ED 50) was determined from plotting the data according to a log dose-response curve. The speed of recovery from paralysis was then estimated by measuring the interval of time between several fixed degrees of twitch tension from 10 to 75% of control (interval 10-75%). Blood samples were simultaneously withdrawn and analyzed to determine the total plasma pancuronium concentration corresponding to 50% of twitch tension (Cp (50)).

Results:

	N	T1/2 α (min)	Pharmacokinetics		
			T1/2 β (min)	V_d _{ss} (l/kg)	Cl (ml/min/kg)
Middle aged	11	11 \pm 6	103 \pm 24	.276 \pm 57	1.9 \pm 0.4
Elderly	13	12 \pm 6	210 \pm 70 [†]	.324 \pm 104	1.1 \pm 0.4 ^{†††}

Group	N	Pharmacodynamics		
		ED 50 (μ g/kg)	Interval 10-75% (min)	Cp (50) (μ g/ml)
Middle aged	9	39 \pm 10	47 \pm 9	0.22 \pm 0.05
Elderly	9	44 \pm 12	75 \pm 16 ^{††}	0.20 \pm 0.06

Mean \pm SD

[†] p < .05 ; significantly different from
^{††} p < .01 ; values in the middle aged
^{†††} p < .001 ; patients

Discussion: Our results indicate that the main pharmacokinetic alteration in the elderly is a decrease in plasma clearance. This slower rate of elimination of pancuronium can be explained by the age-related decrease in renal function. The slower rate of decay of the plasma concentration, due to a 100% prolongation of the elimination half-life, is associated with a longer duration of the effect in the elderly. This study also demonstrates that elderly adults are as sensitive as younger adults to pancuronium.

Conclusion: Pancuronium exerts a prolonged duration of action in the elderly but the dose necessary for adequate initial muscle relaxation is similar to that in younger adults.

References:

1. McLeod K, Hull CJ, Watson MJ: Effects of aging on the pharmacokinetics of pancuronium. Br. J. Anaesth. 51:435-438, 1979
2. Kersten UW, Meijer DKF, Agoston S: Fluorimetric and chromatographic determination of pancuronium bromide and its metabolites in biological materials. Clin. Chim. Acta 44:59-66, 1973