Title: THE HUMAN CUMULATIVE DOSE-RESPONSE OF PIPECURONIUM BROMIDE UNDER BALANCED ANESTHESIA

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Introduction. Pipecuronium Bromide (Arduan) is a bisquaternary nondepolarizing muscle relaxant (MR) in clinical use in Eastern Europe. This study was undertaken to determine the human dose-response of pipecuronium under balanced anesthesia.

Methods. Thirty patients signed informed consents to participate in this study approved by our Institutional Review Board. Patients were premedicated with 50 to 100 mg i.m. meperidine and diphenhydramine, each. Anesthesia was induced with i.v. droperidol, fentanyl, thiopental and N_2O - O_2 administered by face mask. After induction the patients' breathing was manually assisted until intubation. Anesthesia was maintained with increments of fentanyl and N_2O - O_2. The isometric force of contraction of the adductor pollicis muscle elicited by trains of 4 (TOF) 2Hz supramaximal square wave impulses of 0.2ms duration, administered every 10s, through surface electrodes, placed above the ulnar nerve at the wrist, was quantitated by FT10 transducers and continuously recorded. When the depth of anesthesia and T1 (the response to the first of the TOF impulses) became stable an initial dose of 15 µg/kg pipecuronium was injected i.v. After developement of the maximal NM effect of this dose 5 to 10 µg/kg increments were administered whenever the response to the preceeding dose became maximal, until > 90% block developed. At this time patients were intubated. From the computer derived log dose-response regression line the ED50 and ED90 of pipecuronium was determined for each patient. When necessary 15 µg/kg pipecuronium was administered for maintenance of surgical relaxation, whenever T1 recovered to 25% of control. At the end of surgery patients were allowed to recover spontaneously. If at the termination of anesthesia the T4/T1 ratio was < 0.75 the residual NM block was antagonized by the i.v. injection of a mixture of 40 µg/kg neostigmine and 15 µg/kg atropine. The NM effects of pipecuronium were compared to those of vecuronium observed in a similarly premedicated and anesthetized group of patients (1).

Results. The total dose of pipecuronium administered before intubation was 43.5±2.1 (mean± SEM; range 25 to 80) µg/kg. These doses produced > 100% block in 12 and 95.4±0.8 (90.1 to 99.2)% block in 18 patients. T1 returned to control in 25.4±3.5 min. The ED50, ED90, and the clinical duration of 15 µg/kg maintenance doses, and the recovery rate, after the last dose of pipecuronium, are shown in table 1. In 6 of the 30 patients T4/T1 ratios were > 0.75 at the termination of anesthesia. In the other 24 patients, in whom T4/T1 was < 0.75, at this time, the residual NM block was antagonized. The reversal data are summarized in table 2. Pipecuronium injected before intubation decreased the HR from 73.3±2.9 to 67.2±2.5(p < 0.02; paired t test), systolic BP from 124.6±3.8 to 115.1±3.6(NS) and the diastolic BP from 72.2 ±2.1 to 68.6 ±1.7(NS).

Discussion. The data summarized in table 1 indicate that pipecuronium is more potent than vecuronium. The clinical duration of identical 15 µg/kg maintenance doses and the recovery rate of pipecuronium were longer than those of vecuronium. There was a tendency for the prolongation of action of subsequent maintenance doses of pipecuronium. The residual NM block could be antagonized with 40 µg/kg neostigmine. Recovery was faster and more complete when neostigmine was administered when in the course of spontaneous recovery, T1 ≥ 50% than when it was ≥ 37% of control. The moderate decrease of HR observed in this study would indicate that pipecuronium may have a mild stimulating effect on the cardiac vagus. The finding that there is less difference between the recovery of the T4/T1 ratio and that of T1 towards control values (see table 2) than that observed with other nondepolarizing MR (1) suggests that the NM effect of pipecuronium may be mostly postsynaptic.

Table 1. Comparison Of The Neuromuscular Effects Of Pipecuronium And Vecuronium Under Balanced Anesthesia.

	Pipecuronium	Vecuronium	p<*
ED 50 (µg/kg)	20.3±1.1(30)[1]	30.1 (n=18)[2]	
ED 90 (µg/kg)	33.0±1.6(30)	43.7 (n=18)	
Clinical Duration (min)			
1st Dose	41.3±2.9(21)	13.8±0.8(42)	0.001
2nd Dose	52.5±5.4(13)	15.0±0.9(36)	0.001
Recovery Rate (min)	35.9±5.8 (9)	15.4±1.6(39)	0.001

[1]Mean ±SEM of number of observations indicated in parentheses.
[2]Determined with "single dose" method.
*Indicates significance (Student's t test) between corresponding pipecuronium and vecuronium data.

Table 2. Antagonism Of The Residual Pipecuronium Block By Neostigmine (40µg/kg) + Atropine (15µg/kg).

	T1 Before Reversal			
	10 to 37%(n=17)		50 to 100%(n=7)	
	T1	T4/T1	T1	T4/T1
Before Reversal	25.5±1.9[1]	0.04±0.01	74.2±7.0	0.48±0.11
After Reversal				
2 min	47.0±4.2	0.36±0.05	88.3±3.8	0.81±0.06
5 min	67.4±4.2	0.63±0.04	99.4±3.8	0.88±0.03
10 min	82.0±3.8	0.80±0.02	102.9±4.1	0.91±0.02

[1]Mean ±SEM of number of observations indicated in parentheses. Corresponding data in the T1 ≤ 37% and T1 ≥ 50% groups different at the p < 0.01 level.

Reference. 1. Foldes FF, Nagashima H, Boros M et al: Muscular Relaxation With Atracurium, Vecuronium and Duador Under Balanced Anaesthesia. Br J Anaesth 55:97S-103S, 1983.