Title: The dose-response evaluation of pipecuronium bromide in the elderly population under balanced anesthesia

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Introduction: Pipecuronium (PIP) is a new non depolarizing bis-quaternary muscle relaxant under clinical investigation in this country. In young and middle aged patients, PIP has been found to have a neuromuscular blocking action similar to pancuronium but lacking its cardiovascular side effects.[1] Elderly patients may demonstrate a different response to neuromuscular blocking agents[2] and therefore the purpose of this study was to examine the dose-response of PIP in this patient population under balanced anesthesia.

Methods: Thirty ASA Class I-III patients of either sex, ages 65-80 years old gave informed consent to participate in this IRB approved study. After premedication with morphine 0.1 mg/kg and atropine 0.4 mg IM, anesthesia was induced with fentanyl 3-6 µg/kg and thiopental 3-6 mg/kg IV. N_2O and O_2 were administered by face mask in a 60:40 ratio. After induction the isometric force of contraction of the adductor pollices muscle was elicited utilizing a train-of-four(TOF) 0.2 Hz supramaximal square wave impulse of 0.2 milliseconds duration every 10 seconds via surface electrodes over the ulnar nerve. The response was quantitated with a Grass FT10 force transducer and continuously recorded on a Grass polygraph. Once the first response of TOF (T_1) was stabilized PIP 0.015 mg/kg was administered IV. After the development of the maximal neuromuscular effect of this dose, 0.005 mg/kg increments of PIP were administered until T_1 was 15% of control (allowing for maximal effect between doses). Intubation was attempted at least 2 min after the last incremental dose. Log-probit and linear regression analysis of the log dose vs % supression were performed and the ED_{50}, ED_{90} and ED_{95} were determined for each patient by both methods. At least 4 data parts were utilized in the analysis. Data from one patient was not analyzed because of lack of data. If necessary 0.005 mg/kg of pipecuronium was administered to maintain surgical relaxation. Maintenance dose data was not evaluated in this investigation. At the end of the surgery the patients were allowed to recover spontaneously as much as possible before neostigmine 2.5 mg and glycopyrrolate 0.5 mg were administered by IV injection. T_1 as a percent of control was examined immediately before and 2, 5, 8 and 10 minutes after the administration of reversal agent to determine the speed of recovery from neuromuscular blockade. The patients' anesthesia was maintained throughout the reversal period with N_2O/O_2. All values are expressed as mean ± standard deviation.

Results: The patients ranged in age from 68-78 yrs with a mean of 72 ± 3.9 years. There were 7 male and 24 females with a mean weight of 67.2 ± 12.9 kg. The mean ED_{50} ED_{90}, and ED_{95} by probit analysis were 22.2 µg/kg, 31.5 µg/kg and 34.9 µg/kg respectively. (Table I) The mean ED_{50}, ED_{90} and ED_{95} from linear regression analyses of log dose were 22.7 µg/kg, 32.3 µg/kg and 33.0 µg/kg respectively (Table I).

Data demonstrating antagonism of residual neuromuscular block by neostigmine is shown in Table II. Before reversal was administered the patients had demonstrated 39.2 ± 23.7% recovery of T_1 (as compared to T_1 control). Ten minutes after the administration of antagonist recovery had reached 89.8 ± 13.6% of control.

Table I

Mean ED_{50}, ED_{90}, and ED_{95} for pipecuronium by 2 analyses methods

	Log Probit µg/kg	Linear Regression µg/kg	n
ED_{50}	22.2	22.7	30
ED_{90}	31.5	32.3	30
ED_{95}	34.9	33.8	30

Table II

Antagonism of residual neuromuscular blockade

	T_1 as % T_1 control	n
Before reversal	39.2 ± 3.7	30
Time after reversal		
2 min.	59.0 ± 21.8	30
5 min.	77.3 ± 18.3	29
8 min.	85.1 ± 16	28
10 min.	89.8 ± 13.6	27

Discussion: Due to the physiologic changes associated with aging one may anticipate an alteration of response to neuromuscular blocking agents in this population.[3] The data demonstrated in Table I indicates that PIP has an ED_{50}, ED_{90} and ED_{95} similar to the patients examined by Foldes et al.[1] This is similar to the results obtained when pancuronium is compared for dose response in younger and older patients.[4] The duration of effect of the original and maintenance doses was not measured. However when pancuronium's duration of effect is compared in the young and elderly patient, the duration is longer in the elderly despite similar ED_{90}'s.[4] This can probably be explained on a pharmacokinetic basis. Recovery data demonstrated that residual neuromuscular blockade can be rapidly antagonized with 2.5 mg of neostigmine resulting in 89% recovery of T_1 in 10 minutes. In conclusion, it appears that the ED_{50} and ED_{90} of PIP is similar in the young and geriatric population.

References

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