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TITLE: INTERACTION OF ANTIBIOTICS ON PIPECURONIUM INDUCED NEUROMUSCULAR BLOCKADE

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Pipecuronium bromide is a long-acting steroidal neuromuscular blocking agent without cardiovascular side-effects. Its chemical structure is similar to that of pancuronium bromide (1). There is experimental evidence of interactions between some antibiotics and non-depolarizing muscle relaxants (2). This prospective, randomized study looks at the interaction of pipecuronium and two antibiotics (clindamycine, colistin), administered at 25% recovery of neuromuscular blockade.

The study was approved by the Institution's Ethical Committee. Following informed consent, sixty adult patients (between 15-61 years of age, ASA I-II), not taking any medication, were studied during gynecologic and gastroenterologic interventions. The patients were assigned to three treatment groups each of twenty patients, receiving either placebo, colistin or clindamycine. Anesthesia was induced with propofol (2,5 mg/kg BW) and alfentanil (25 µg/kg) I.V. and maintained with a propofol infusion (8 mg/kg/h) and 60% nitrous oxide in oxygen. Electromechanical neuromuscular monitoring was performed using the Myograph 2000® (Biometer) with supramaximal stimulation of the ulnar nerve at the wrist at a rate of 1 Hz. A preload tension of 200 g was applied to the thumb. After a stable baseline response was achieved during at least 2-5 min, pipecuronium was administered I.V. in a dose of 50 µg/kg (ED_{95}) and the response curve of the thumb contraction registered. Two minutes later the patient was intubated; top-up doses of 1/4 ED_{95} dose were administerd when needed. The antibiotic was given at 25% recovery of the twitch response, and the time to 75% recovery was recorded. If recovery was less than 100% at the end of anesthesia, neostigmine was administered. Recovery time from 25% to 75% was compared between patients receiving placebo or the antibiotics (clindamycine, colistin, controls). Results (table) are expressed as mean values ± S.D.. Statistical analyses were performed using Student's t test. $P \leq 0.05$ was considered significant.

recovery	Control (min)	Clindamycine (min)	Colistine (min)
0 - 25 %	24 ± 9	22 ± 7	28 ± 11
25 - 50 %	18 ± 10	24 ± 14	31 ± 18*
25 - 75 %	34 ± 15	50 ± 30*	78 ± 44***
50 - 75 %	19 ± 9	27 ± 20	51 ± 30***

*P < 0.05, ***P < 0.001 compared to control.

In conclusion: administration of both clindamycine and colistin results in a statistically significant prolongation of the recovery time of a pipecuronium induced neuromuscular block. However, the prolongation is more pronounced after colistin.

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2) Ann Rev Pharmacol 1972; 12: 169-184

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TITLE: PHARMACOKINETICS OF PIPECURONIUM IN INFANTS, CHILDREN AND ADULTS

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INTRODUCTION: Pipecuronium bromide (P) is a new long acting non-depolarizing steroidal muscle relaxant caracterized by similar neuromuscular (NM) blocking action and pharmacokinetics to pancuronium in adults (1). The duration of action of ED_{95} of P is similar in adults and children, but shorter in infants (2,3). In order to evaluate our hypothesis that the difference in NM blocking effect of P in infants may be explained by age-related differences in the pharmacokinetics of P, we investigated and compared the pharmacokinetics of pipecuronium in infants, children and adults.

METHOD: After institutional approval and informed consent, six infants (1-12 months), 5 children (2-9 years) and 7 adults (18-62 years) ASA class 1 or 2 were entered into the study. In the pediatric patients, anesthesia was induced with thiopental 5 mg/kg, alfentanil 15 µg/kg i.v. and maintained with N_2O (60%) in O_2 supplemented with repeated doses of alfentanil. In the adult patients 3-5 mg/kg thiopental, 1-2 µg/kg fentanyl, N_2O (60%) in O_2 and isoflurane 0.8-1.0% were used. The trachea was intubated without muscle relaxant. When conditions were stable, two times ED_{95} of P was injected rapidly i.v. Arterial blood was sampled before and following P administration at intervals increasing from 2 to 30 minutes for the next 300-360 minutes.
Blood was placed in heparinized tubes and immediately centrifuged. Plasma samples were quickly frozen and stored at -70°C until P content was quantified by a new method using ^{125}I labeled rose bengal allowing for the quantification of P at concentrations as low as 5 ng/ml (4). Data were analyzed by non-linear regression and described by a 2-compartment open model. ANOVA followed by a Duncan's multiple comparisons test was employed for statistical comparison between the groups.

RESULTS: Compared to adults, in infants P had a more rapid distribution half-live (t1/2 alfa), a slower elimination half-live (t1/2 ß) and a smaller plasma clearence (Cl). In children and infants t 1/2 alfa of P was similar, but t1/2 ß was longer in infants. Plasma concentrations of P extrapolated to time 0 in the two compartements are given in table 1. defined as A and B, and B beeing lower in infants than in children.

Table1. Comparison of pharmacokinetic variables

Variables	infants	children	adults
t1/2 alfa (min)	2.19±1.45*	1.89±0.90*	6.0±2.9
t1/2beta (min)	125±63*†	59.3±19.5	62±16
Cl (ml/min/kg)	1.29±0.54*	2.07±0.62	2.17±1.0
V_{dss} (ml/kg)	194±51	171±56	226±63
AUC(µg/ml/min)	93.8±50.6*	75±25	50.8±18.4
A (µg/ml)	2.83 ±1*	4.72±1.75*	1.55±0.16
B (µg/ml)	0.42±0.1†	1.0±0.22	0.55±0.2

mean±se; *P<0.05 compared to adults; †P<0.05 between infants and children
AUC= area under curve; Vdss= volume of distribution in steady state

DISCUSSION: In the present study half-lives of P in adults were shorter than previously reported (1,5). This may be explained by the fact that contrary to other studies, P concentration was measured in the arterial blood. Pharmacokinetic profile of P in infants, such as the rapid fall of initial plasma concentration, may partly be responsible for the shorter clinical duration of P in infants, as reported when 1x ED_{95} doses have been used (3). The longer t1/2 ß of P in infants however, may result in prolonged NM blockade when elevated or repeated doses are administered.

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