Title: PHARMACOKINETICS OF NEOSTIGMINE IN ANESTHETIZED INFANTS AND CHILDREN

Authors: DM Fisher MD, R Cronnelly MD PhD, RD Miller MD, M Sharma PhD

Affiliation: Department of Anesthesia, University of California, San Francisco, California 94143

Introduction. Despite many studies of the response of infants and children to muscle relaxants, the antagonists have received little attention. Thus, we determined the pharmacokinetics of neostigmine in anesthetized infants and children and compared these results with known values for adults.

Methods. Six patients were studied after obtaining approval of the committee on human research and informed consent. The patients were divided into two groups by age: infants, less than one year (n = 3), and children, greater than one year (n = 3). Anesthesia was maintained with 70% N_2O and halothane, 0.6% end-tidal as measured by mass spectrometry. End-tidal PCO_2 was maintained at 30-40 mmHg and nasopharyngeal temperature maintained at 35-37° C. Supramaximal 0.15 ms stimuli were administered to the ulnar nerve at 0.15 Hz and the response of the adductor pollicis was measured with a Grass FT-10 transducer. d-Tubocurarine was administered by bolus until twitch tension was depressed 90%. Neostigmine, 100 µg/kg for infants and 70 µg/kg for children, and atropine, 30 µg/kg, were then administered as a 2 min intravenous infusion. The larger dose for infants was selected after preliminary studies demonstrated a short detection period. Blood samples were obtained before the infusion and at 0,2,4,6,8,10,15,20,25,30, 45,60,90,120,150,180,210 and 240 min after drug administration. The samples were stored at -70° C until assayed for neostigmine using a high-pressure liquid chromatographic technique that separates parent compound from metabolites(1). This assay is sensitive to 1.0 ng/ml and has a coefficient of variation of < 5%. The neostigmine concentration time curve was fitted to a two compartment open pharmacokinetic model. The following parameters were determined using standard formulas: $t\alpha 1/2$, distribution half-life; $t\beta 1/2$, elimination half-life; V1, volume of the central compartment; Vdss, steady-state distribution volume; and Cl, total plasma clearance. We compared these data with known values for adults obtained under comparable conditions(2). Because of the small sample size, we combined infants and children into one pediatric group and compared them to adults using the Mann-Whitney U test ($P < 0.05$).

Results. As in adults, neostigmine could be identified in serum until 130-213 min after drug administration. Kinetic parameters were similar for infants and children. $t\alpha 1/2$ and $t\beta 1/2$ were shorter, V1 smaller, and Cl higher in infants and children than in adults (Table 1). There was no difference in Vdss. Neuromuscular blockade was fully reversed in all patients.

Discussion. In pediatric patients, dosage recommendations for neostigmine range from 20-80 µg/kg, 70 µg/kg being the dose most frequently recommended(3). This is approximately twice the recommended adult dose. Our results indicate that neostigmine levels will be higher in infants and children than in adults immediately after administration although they fall more rapidly in pediatric patients during both distribution and elimination. No pharmacodynamic model is available for neuromuscular antagonists; however, the rapid half-lives and high clearance may explain the higher dosage recommendations for neostigmine in infants and children compared to adults.

References.

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2. Cronnelly R, Stanksi DR, Miller RD, et al: Renal function and the pharmacokinetics of neostigmine in anesthetized man. Anesthesiology 51:222-226, 1979

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Table 1. Pharmacokinetic Parameters (Mean ± SD)

	$t\alpha 1/2$ (min)	$t\beta 1/2$ (min)	V1 (l/kg)	Vdss (l/kg)	Cl (ml/kg /min)
Adults@ (n=7)	3.4 ±1.1	81 ±49	.20 ±.03	.76 ±.23	8.8 ±2.6
Total# pediatric population (n=6)	1.2* ±0.6	39* ±12	.09* ±.05	.50 ±.18	12.6* ±2.4
Infants (n=3)	1.3 ±0.7	37 ±1	.09 ±.04	.54 ±.11	13.3 ±1.9
Children (n=3)	1.2 ±0.7	40 ±18	.08 ±.07	.45 ±.26	11.9 ±3.0

Includes infants and children

* Different from adults ($P < 0.05$) by Mann-Whitney U test

@ From previous study(2)