Title: PHARMACOKINETICS AND PHARMACODYNAMICS OF NEOSTIGMINE IN THE ELDERLY

Authors: W.L. Young, M.D., W. Backus, M.D., R.S. Matteo, M.D., E. Ornstein, M.D., and J. Diaz

Affiliation: Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, and The Presbyterian Hospital, New York, New York 10032

Introduction. Previous studies have shown that the prolonged duration of neuromuscular blockade with d-tubocurarine, metocurine, and pancuronium in the elderly is a consequence of delayed elimination and a smaller volume of distribution of the relaxant rather than differences in the plasma concentration-response relationship.[1,2] This study was undertaken to assess differences between young and elderly patients with respect to antagonism of stable neuromuscular blockade by neostigmine.

Methods. Five elderly patients (ages 71-80) and seven younger patients (ages 34-56) scheduled to undergo elective craniotomy were included in the study after obtaining institutional approval and informed consent. All patients had normal renal and cardiac function. Anesthesia was induced with thiopental, and tracheal intubation was facilitated with succinylcholine (Sch). Anesthesia was maintained with N_2O:O_2 (60:40%) in addition to 1 MAC halothane, the inspired concentration adjusted for age. Mechanical ventilation maintained moderate hyperventilation ($PaCO_2$, 25-35 torr) and esophageal temperatures were maintained at 34.5 - 36°C. Neuromuscular transmission was assessed by quantitating the height of evoked compound electromyographic (ECEMG) potentials of the adductor of the thumb in response to supramaximal stimulation of the ulnar nerve from a Grass S8 stimulator. Responses to single stimuli of 0.2 ms duration delivered at a frequency of 0.1 Hz (6/min) were recorded. Alfter Sch administration, return of stimulus height to normal was assessed by train-of-four stimulation. A bolus of 0.1 mg/kg of metocurine was given, followed by a continuous infusion of metocurine to achieve 90% paralysis. After at least 30 min of observation, to ensure constant stimulus height, a bolus of neostigmine (0.07 mg/kg) and atropine (0.02 mg/kg) was given intravenously. Heparinized blood samples were drawn from a contralateral arterial catheter at 1, 3, 5, 10, 20, 30, 45, 60 min, and 1.5, 2, 2.5, 3, 3.5 and 4 hr. Plasma was separated and frozen until assayed by high performance liquid chromatography (HPLC), sensitivity 0.1 ng/ml.

Plasma concentration-response curves were fitted by using least squares nonlinear regression. Pharmacokinetic parameters were determined by using a method for bolus iv injection of a drug. Following injection of neostigmine, the following times of recovery from neuromuscular blockade were recorded: start of recovery, 50% recovery, maximum recovery and duration of maximal response. As response to neostigmine diminished, additional samples were drawn if any significant change in response was observed that fell between kinetic sampling times. The log-plasma concentration-response curves were constructed for the linear portion of the plasma concentration-response curve between 20 and 80% paralysis for each patient and the concentration of neostigmine at 80, 50 and 20% paralysis was calculated. Comparisons between the pharmacokinetic and pharmacodynamic parameters were compared by applying Student's t-test for unpaired data (two-tailed).

Results. Plasma decay curves for neostigmine in both groups are best described by a bi-exponential equation. The relationship for the elderly is described by the equation $C = 1.34e^{-0.94t} + 0.09e^{-0.042t}$ and for the younger group $C = 0.73e^{-0.95t} + 0.087e^{-0.068t}$ where C is μg/ml and t is min. The pharmacokinetic data are presented in Table 1. Recovery times and duration of response are in Table 2. There is no significant difference between the log plasma concentration-response data for either group.

Discussion. In general, our pharmacokinetic data agree with those of Williams who observed a very rapid decrease in the plasma concentration of neostigmine reflected in a brief elimination half life.[3] This is in contrast to Cronnelly who reported a much longer elimination half life in normal patients.[4] In this study, the duration of maximum response to neostigmine was found to be significantly prolonged in the elderly compared to younger patients (Table 2). This cannot be attributed to a difference in pharmacodynamics, as there was no significant difference in response to neostigmine compared with plasma concentration of the drug. The only significant difference in pharmacokinetic parameters is a smaller initial volume of distribution (V_i) in the elderly group. Since the V_i of neostigmine exceeds the plasma volume, it most likely includes the extracellular fluid volume (ECF). The ECF is known to be smaller in the elderly than in the young.[5] The observed decrease in V_i in the elderly reflects the greater concentration of neostigmine initially available to act at the neuromuscular junction. This observation could explain the prolonged duration of maximum response to neostigmine seen in our elderly group.

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References.

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Table 1. Pharmacokinetic Parameters (Mean ± SE)

	Young, n=7 (34-56 yrs)	Elderly, n=5 (71-80 yrs)	P
$t_{1/2}$ elim (min)	18.5 ± 7	16.7 ± 0.8	NS
Clp ($ml \cdot kg^{-1} \cdot min^{-1}$)	33.5 ± 4	23.4 ± 5	NS
V_i (l/kg)	.10 ± .04	.068 ± .018	<.05
Vd_{area} (l/kg)	.549 ± .12	.566 ± .13	NS

Table 2. Response Times (Min, Mean ± SE)

	Young, n=7 (34-56 yrs)	Elderly, n=5 (71-80 yrs)	P
Onset of Response	0.52 ± .008	0.77 ± 0.1	NS
Maximum Response	6.7 ± 1.3	6.7 ± 1.4	NS
Duration of Maximum Response	13.14 ± 2.4	42 ± 10	<.01