Title: PHARMACOKINETICS AND PHARMACODYNAMICS OF METOCURINE IN INFANTS, CHILDREN AND ADULTS

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Introduction. Muscle relaxant kinetics are altered in infants. This has been shown with d-tubocurarine (dTc), atracurium, and vecuronium,[1] three relaxants with both renal and nonrenal routes of elimination. The purpose of this study was to examine the pharmacokinetics in infants of metocurine (MTc), a muscle relaxant eliminated entirely by the kidney.

Methods. A total of 19 neurosurgical patients were studied after obtaining informed consent with institutional review board approval. Patients were assigned to 1 of 3 groups based on age: infants, 1-12 months (n=5); children, 1-9 years (n=7); and adults, 19-68 years (n=7). Anesthesia was induced with thiopental and/or halothane. Following induction, anesthesia was maintained with 1% halothane and 60% nitrous oxide in oxygen. After arterial catheter placement, a single intravenous dose of MTc (0.2 mg/kg) was given. The ulnar nerve was stimulated at the wrist through surface electrodes from a Grass stimulator. A supramaximal square wave impulse of 0.2 msec duration at a frequency of 0.1 Hz was used. The evoked compound electromyograph (ECEMG) signal was monitored at the adductor muscles of the thumb. The signal was processed by a Gould waveform recorder/amplifier. Blood samples were obtained from the arterial catheter at 1, 3, 5, 10, 15, 25, 35, 45, 60, 120, 180, and 240 minutes. The plasma was separated and frozen until analyzed for MTc by radioimmunoassay. Time-concentration curves and kinetic parameters were derived for bolus iv injection of a drug. The log plasma concentration-response curves for adults, children and infants were generated after probit analysis and compared by analysis of covariance. A regression of log plasma concentration-probit ECEMG was calculated for each patient, from which the estimated plasma concentration for 50% ECEMG depression (Cp_{50}) was derived. The dose needed for 50% ECEMG depression (D_{50}) was calculated from the product of Vd_{area} and Cp_{50}. The pharmacodynamic and pharmacokinetic parameters were compared by ANOVA followed by the Bonferroni inequality for t-tests. $P < 0.015$ was considered significant.

Results. Plasma decay curves for MTc in all groups were best described by biexponential equations. The kinetic and dynamic parameters are summarized in Table 1. The slopes and elevations of the log concentration-ECEMG curves were not significantly different.

Discussion. Vd_{area} was found to be significantly greater in infants than in adults. This may be a reflection of an increased extracellular volume. As a result, the elimination half-life ($t_{1/2}$ elim) was significantly prolonged in infants compared with children ($P < 0.001$) and tended to be longer than in adults ($P = 0.0565$); this occurred even though there was a significant increase in the plasma clearance for infants. Fisher's studies of vecuronium in infants demonstrated an increase in Vd_{area} but no change in $t_{1/2}$ elim or Clp.[2] In studies of dTc in infants, Clp has been reported to be either decreased or unchanged, while Vd_{area} was unchanged.[3,4] It is unclear why infants and children had a greater Clp in the present study.

Despite age-related differences in pharmacokinetics, no changes in pharmacodynamics were found between the groups. Consequently, Cp_{50}, D_{50} and recovery index were not statistically different between groups. Goudsouzian et al[5] have also found no difference in recovery times for MTc in infants and children.

In summary, this study has shown the pharmacokinetics of MTc differs significantly in infants with respect to volume of distribution, plasma clearance, and elimination half life. There was no significant difference in the plasma concentration-response relationship, the recovery index, or the D_{50} for the three groups.

References

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4. Matteo RS, Lieberman IG, Salanitre E, et al: Anesth Analg 63:799-804, 1984
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Table 1. Pharmacokinetic/Dynamic Parameters (Mean ± SD)

	Infants (n = 5)	Children (n = 7)	Adults (n = 7)
V_i (L/kg)	0.134±.082	0.106±.040	0.090±.018
Vd_{area} (L/kg)	0.767±.214*	0.509±.157	0.360±.066
Clp ($ml \cdot kg^{-1} \cdot min^{-1}$)	3.3±0.6†	3.4±0.7†	2.1±0.4
$t_{1/2}$ elim (min)	162±46§	103±23	121±19
† 25-75% recovery (min)	62±9	50±30	70±60
Cp_{50} (ug/ml)	0.073±.052	0.247±.108	0.329±.216
D_{50} (mg/kg)	0.062±.047	0.114±.020	0.109±.070

† 25-75% = time for recovery from 25-75% of control ECEMG.
*$P < 0.001$, †$P < 0.005$, compared to adults. §$P < .015$, compared to children.