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Title : d-Tubocurarine Concentration and Neuromuscular Blockade in the Neonate

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Introduction. The fate of muscle relaxants in neonates is of particular interest since it has been reported that their response to a nondepolarizing muscle relaxant, d-tubocurarine (dTc), is quite different from that of older infants, children and adults. Neonates have been observed by Stead and Bush to be unusually sensitive to the action of dTc.[1, 2] In contrast, Churchill-Davidson suggested that prolonged effects of dTc in neonates were due to overodose.[3] Goudsouzian et al[4] determined the effect of dTc by twitch response in infants and children. They found infants and children more resistant to dTc and recovered faster than adults from a similar level of neuromuscular depression. In the present study, plasma concentration of dTc is correlated with neuromuscular transmission as measured by the evoked compound electromyelograph (ECEMG) of the adductor muscle of the thumb in neonates and compared with data obtained from infants, children and adults.

Methods. Four groups of neurosurgical and general surgical patients have been studied after obtaining informed consent. The groups are neonates, 0-1 mo (n = 5); infants, 1-12 mos (n = 6); children, 1-4 yrs (n = 6) and adults (n = 8). Premedication consisted of secobarbital (20-100 mg) and atropine (0.1 - 0.5 mg) in the infants, children and adults. Neonates received either no premedication or atropine 0.1 mg. Anesthesia was induced with either thiopental or halothane. A nitrous oxide-halothane mixture was used for tracheal intubation and maintenance of anesthesia.

Prior to administration of dTc, the patient's arm was fixed to an armboard. A needle was placed overlying the adductor muscle of the thumb to detect the ECEMG. The ulnar nerve was stimulated at the wrist or elbow with surface electrodes by a supramaximal stimuli from a Grass stimulator. Responses to single stimuli of 0.2 msec duration delivered at a frequency of 0.1 Hz (6/min) were observed. A stable baseline of ECEMG was recorded for 10 min, then the iv dose of dTc (0.3 mg/kg) was given. As the ECEMG response to single stimuli returned, blood samples were withdrawn to be analyzed for dTc by radioimmunoassay. Time intervals were noted for 50% return to control ECEMG.

Results. There was a highly linear correlation between the plasma concentration of dTc and the ECEMG response (Fig 1). The formulae for the regression lines where x is percent recovery of response in ECEMG and y, plasma concentration of dTc were: adults, $y = 1.0058 - .0071x$, $r = -0.78$; children, $y = 1.057 - .0076x$, $r = -.77$; infants, $y = 0.8243 - .0052x$, $r = -.80$; significance was tested by analysis of variance. F was calculated for each group. There was no significant difference between these three groups. The neonates appeared to fall into two patterns. In three neonates, the regression line was not significantly different from that of the adult, child and infant, the regression formula being $y = .8896 - .0068x$, $r = -.81$. The other two required much higher concentrations of dTc to depress neuomuscular transmission, the regression formula being $y = 3.281 - .0168x$, $r = -.83$. Following dTc 0.3 mg/kg, the time for 50% return of stimulus height was: adults 55 ± 6 min (mean ± SE); children 43 ± 7 min; infants 66 ± 18 min; neonates 72 ± 10 min. When these times were compared, the neonates' time for 50% return of ECEMG stimulus height was of borderline significance compared with the adult values, $.05 < P < .1$.

Discussion. Goudsouzian et al[4] found infants and children more resistant to dTc and recovered faster than adults from a similar level of neuromuscular depression. O'Keeffe's[5] finding of a shorter elimination half-life and increased clearance of dTc in infants and children complements Goudsouzian's study. Our study shows no difference in the sensitivity of the myoneural junction of infants, children or adults to dTc. The difference reported by Goudsouzian is undoubtedly related to the distribution and elimination of dTc. The reason two of the neonates required a significantly higher serum concentration of dTc to depress neuromuscular transmission than the other three is not clear. It does not appear to be related to differences in gestational age or physical status. The finding that the time of recovery of 50% of ECEMG appears longer in neonates than in adults may be related to the urinary excretion of dTc. The newborn's renal function (glomerular filtration rate, renal plasma flow), based on body surface area is 30-40% of the adult dose. Since urinary excretion is the main route of elimination of dTc from the body, a decrease in excretion would prolong the effect of the drug.

References

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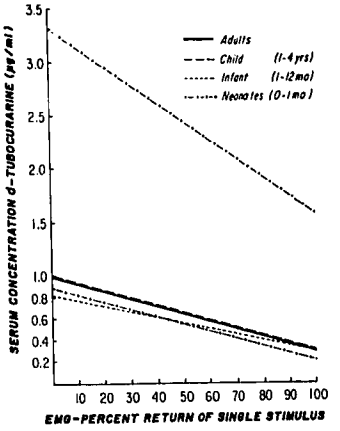

Fig 1. Regression lines for the four groups of patients. There are two regression lines for neonates.