Title : CURARE NEUROMUSCULAR BLOCKADE DURING HYPOTHERMIA IN MAN

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Introduction. In cats hypothermia reduces the elimination of d-tubocurarine (dTC) from serum into urine and bile but increases the serum concentration of dTC necessary to achieve neuromuscular blockade (NMB). The net effect may be prolongation of NMB following administration of dTC depending on the temperature.[1] The effect of hypothermia on the pharmacokinetics (distribution and elimination) and pharmacodynamics (drug concentration - effect relationship) of dTC in humans was studied in patients undergoing craniotomy for intracerebral tumor resection or aneurysm clipping.

Methods: Thirteen patients were studied with informed consent and approval of the Committee on Human Research, UCSF. Six patients had craniotomy during thiopental, halothane (0.5-0.7% end-tidal), N_2O (60%) anesthesia with controlled hyperventilation (pCO_2 25 torr). Body temperature was measured with distal esophageal and hypothenar muscle probes (Yellow Springs) and reduced by surface cooling to a mean of 31.1°C. Seven patients had elective peripheral procedures under the same type of anesthesia except that ventilation was controlled to maintain a pCO_2 of approximately 40 torr and body temperature was maintained at a mean of 35.5° C. Force of thumb adduction was measured with a force transducer in response to supramaximal (0.15 msec duration, 0.15 Hz) ulnar nerve stimulation at the wrist. After the desired temperature was achieved and stable, dTC was administered by infusion pump at a rate of approximately 17 ug/kg/min for approximately 10 minutes or until 80-90 percent NMB had been achieved. Blood was sampled every minute for 10 minutes during the infusion, every 2 minutes for 10 minutes and every 15 minutes thereafter and assayed for dTC by radioimmunoassay.

Plasma concentrations were fit to a 2 compartment model using a nonlinear least squares regression program[2]. The following pharmacokinetic parameters were calculated: distribution (α) and elimination (β) half-lives (t 1/2), volume of the central compartment (V_1), volume of distribution at steady state (Vdss) and plasma clearance rate (Cl). The effect data were fit to a pharmacodynamic model previously described[2] to estimate the following pharmacodynamic parameters:

t1/2 Keo - half time for equilibration between dTC plasma concentration and NMB, an estimate of neuromuscular junction perfusion.

Cpss(50) - steady state plasma concentration that results in 50 percent NMB, an estimate of neuromuscular junction sensitivity to dTC.

Results:

Parameter	Hypothermia (31.1°C)	Control (35.5°C)
t 1/2 α (min)	4.2±1.5	6.4±2.6
t 1/2 β (min)	89±24	104±56
V_1 (ml/kg)	55±13*	101±36
Vdss (ml/kg)	229±50	289±105
Cl (ml/kg/min)	2.1±0.7	2.5±0.6
t 1/2 Keo (min)	9.13±4.4**	6.0±1.2
Cpss(50) (ug/ml)	.54±.20*	.36±.04

mean±S.D. *p<.05, **p = .09

There was a significant decrease in the volume of the central compartment and increase in plasma concentration required for NMB during hypothermia. There was a trend for the onset of NMB (t 1/2 Keo) to be delayed during hypothermia but this was only significant at the .09 level. There were no pharmacokinetic differences during hypothermia other than the reduced volume of the central compartment.

Discussion. Hypothermia affects the pharmacokinetics of dTC by decreasing the volume of the central compartment. Since clearance and terminal elimination half life are not affected, the duration of dTC NMB would be unaffected relative to normothermia. Hypothermia affects the pharmacodynamics by decreasing the rate at which the plasma concentration of dTC equilibrates with the neuromuscular junction. This results in a delayed onset and may be due to decreased perfusion from vasoconstriction. Hypothermia also decreases the sensitivity of the neuromuscular junction to dTC.

Conclusions. During hypothermia in humans receiving dTC under general anesthesia the following may be observed:

(1) a delayed onset of NMB
(2) higher doses of dTC than usual to achieve NMB
(3) no change in rate of recovery of neuromuscular function

During hypothermia it is recommended that dTC be administered utilizing a peripheral nerve stimulator and allowing for increased lag time from injection to NMB (5-10 minutes).

References.

1. Ham J, Miller RD, Benet LZ, et al: Anesthesiology 49:324-329, 1978
2. Stanski DR, Vozeh S, Sheiner LB, et al: Clin Pharmacol Ther 25:358-371, 1979