Correspondence

Serum *d*-Tubocurarine Concentration and Twitch Height

To the Editor:—In a recent issue, the conclusions of Matteo, Spector and Horowitz[1] that the neuromuscular effects of *d*-tubocurarine were related to serum *d*Tc concentrations were questioned.[2,3] The issue arose from observations of Feldman and Tyrell[4] on the effects of *d*Tc given intravenously into an arm which was isolated from the central circulation by a tourniquet.

Specifically, Feldman and Tyrell injected *d*Tc into an isolated arm, allowed three minutes for equilibration, and then released the tourniquet. The twitch response took about 15 minutes to recover from 25 per cent of normal to 75 per cent of normal. Feldman and Tyrell concluded that if the effect of *d*Tc were related to the plasma concentration, recovery would be faster. However, the observations are not at all out of line with the conventional views of neuromuscular physiology and pharmacology.

Resting muscle blood flow is about 3 ml/100 g/min. This amounts to 1.5 ml plasma/20 g extracellular fluid. Since *d*Tc is limited to the extracellular space (the drug is charged and therefore will not get into cells), the rate of washout would be 1.5/20 × 100 or 7.5 per cent per minute. The half-life for decrease of concentration then would be about 10 minutes.

Feldman observed not concentration but twitch height. These twitch responses must be converted into equivalent *d*Tc concentrations. Measurements of margin of safety allow us to do this: when the twitch response is 25 per cent of normal, about 90 per cent of the receptors are blocked by *d*Tc.[5]

To interpret this fraction of receptors blocked, y, in terms of concentration of *d*Tc, [*d*Tc], one can invoke the usual[6] expression:

$$y = \frac{[d\text{Tc}]}{[d\text{Tc}] + K_B} \qquad (1)$$

(where K_B is the *d*-tubocurarine–receptor dissociation constant). In the present case with 90 per cent of the receptors blocked, $y = .9$, and solving for [*d*Tc] gives a value of 9 times K_B.

Similarly, when the twitch response is 75 per cent of normal, 75–80 per cent of the receptors are occupied. The concentration of *d*Tc at the neuromuscular junction would then be 3–4 times K_B.

That is, during recovery from 25 to 75 per cent of normal twitch height the *d*Tc concentration would decrease from about $9 \times K_B$ to about 3 or $4 \times K_B$—a decrease of more than 50 per cent. Thus, the time taken for the washout should be somewhat greater than the half-life of the drug. That is just what Feldman observed, *i.e.*, Feldman's observations present no reason to reject or alter the classic model of neuromuscular pharmacology.

In passing, it is interesting that Matteo's observations fit beautifully with experimental observations elsewhere. *d*-Tubocurarine has a K_B of about 10^{-7} M (the value has not been measured in man so I'll use an estimate from guinea pig experiments[7]). Matteo *et al.* reported concentrations of 0.7 μg/ml or 10.3×10^{-7} M when the twitch response started to recover and 0.2 μg/ml or 2.94×10^{-7} M when recovery was complete. Equation 1 then tells us that 91 and 74 per cent of receptors were blocked. These values fall right in line with those reported by Paton and Waud[5] in their original measurements of the margin of safety.

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Hypothermia

HALOTHANE, ETHER, AND PROFOUND HYPOTHERMIA Healthy adult mongrel dogs were studied to evaluate differences between two anesthetic techniques used during profound hypothermia in elective circulatory arrests. The animals were surface-cooled to 18 C and then subjected to 30 minutes of circulatory occlusion. Anesthesia was provided with either halothane or diethyl ether. In each group, the anesthetic was administered with either 100 per cent oxygen or 95 per cent oxygen–5 per cent CO_2. Normothermia was re-established by either surface or perfusion rewarming. All five animals receiving halothane–O_2 and perfusion rewarming developed motor disorders. Of ten dogs inhaling 95 per cent O_2–5 per cent CO_2 during rewarming (half the animals with surface and half with perfusion rewarming), only one had a motor disturbance postoperatively. Animals receiving diethyl ether anesthesia evidenced no motor disorder no matter what the technique of rewarming and regardless of whether CO_2 was added to the gas mixture. The authors conclude: 1) it is mandatory to avoid respiratory alkalosis when deep hypothermia is accompanied by halothane anesthesia; 2) at least in this animal model, anesthesia with halothane is inferior to that provided by diethyl ether. (*Sato S, and others: A comparative study of the effect of carbon dioxide and perfusion rewarming on limited circulatory occlusion during surface hypothermia, under halothane and ether anesthesia. Ann Surg 180:192–197, 1974.*) ABSTRACTER'S COMMENT: Does addition of carbon dioxide help by preventing the Bohr shift of the hemoglobin-dissociation curve or by increasing cerebral perfusion? Steward DJ, *et al* (Can Anaesth Soc J 21:15–22, 1974) report data on 25 infants operated upon with profound hypothermia. The anesthesia was halothane–N_2O; during cooling 5 per cent CO_2 was added to the inspired gas mixture. One patient (with a history of previous seizures) was neurologically intact after operation but became comatose in the late postoperative period. The other 24 infants had no neurologic difficulties.