

Cerebrospinal Fluid Levels of *d*-Tubocurarine in Man

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Using radioimmunoassay, *d*-tubocurarine (*d*Tc) was found in the cerebrospinal fluid (CSF) of man after intravenous injection. When *d*Tc was administered in a single dose (0.3 mg/kg) to nine patients, small quantities, $3.5 \pm .26$ ng/ml (mean \pm SE), appeared in the lumbar CSF within 5 minutes. The concentration of *d*Tc in the CSF remained constant for the next 25 minutes, but then began to increase with time to 9.3 ± 4.4 ng/ml 30 minutes after injection, 14.5 ± 4.4 ng/ml at one hour, and 24.9 ± 6.5 ng/ml at six hours. In another group of six patients, three doses of *d*Tc (0.3 mg/kg) were given at 90-minute intervals. Concentration of *d*Tc in the CSF increased after each injection. The quantities of *d*Tc found in the CSF are unlikely to produce any pharmacologic or adverse effect (e.g., convulsion) in man. (Key words: Neuromuscular relaxants, *d*-tubocurarine; Cerebrospinal fluid; Measurement techniques, radioimmunoassay.)

d-TUBOCURARINE (*d*Tc) has been shown to cause marked central nervous system excitation in animals when directly applied to the cerebral cortex or injected into the hippocampus or the lateral ventricle.¹⁻⁶ The absence of such responses when *d*Tc is injected intravenously has been attributed to the impermeability of the blood-brain barrier to *d*Tc. Dal Santo, however, has shown in dogs that following the intravenous injection of radiolabeled dimethyltubocurarine, small amounts were detected in the cerebrospinal fluid (CSF).⁷

Recently, Horowitz and Spector⁸ developed a highly sensitive, specific radioimmunoassay for *d*Tc that can measure as little as 5 ng/ml *d*Tc in serum and 1 ng/ml *d*Tc in CSF. Employing this assay, we have demonstrated in man that intravenously administered *d*Tc does pass into the CSF in very small amounts.

Methods

Two groups of patients were studied to determine the passage of *d*Tc into the CSF following single

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or repeated intravenous injections of this drug. In the first group (single dose of *d*Tc) nine patients were studied during anesthesia for craniotomy for cerebral aneurysms, arteriovenous malformation, or pituitary tumors. Preanesthetic medication consisted of secobarbital, 50-100 mg, and atropine, 0.4-0.6 mg. Anesthesia was induced with thiopental, 200-275 mg. Moderate hyperventilation was maintained throughout by a mechanical ventilator. Partial pressures of carbon dioxide in arterial blood were measured in five patients and ranged from 24 to 28 torr. In all patients anesthesia was maintained with a mixture of nitrous oxide, 60 per cent, inspired, and halothane, 0.5-0.9 per cent, inspired.

Following induction of anesthesia, each patient was placed in the lateral position and a catheter was introduced into the lumbar subarachnoid space through a 16-gauge Huber needle for intracranial neurosurgical indications. The patients were then repositioned for the operation. Central venous pressure and/or intra-arterial lines were placed as required for clinical monitoring. *d*Tc, 0.3 mg/kg, was then administered intravenously. CSF samples (0.5-1.0 ml) were obtained 5, 10, 15, 20, 30, 60, and 90 minutes, and two, three, four, five, and six hours later. In a few patients, samples were obtained as long as ten hours following injection of *d*Tc. The deadspace of the subarachnoid catheter was 1 ml, and this volume was discarded before each CSF sample was obtained. Blood samples (2-3 ml) were obtained simultaneously from either indwelling arterial or central venous pressure catheters for measurement of serum *d*Tc concentrations.

A second group (repeat doses of *d*Tc) consisted of six neurosurgical patients undergoing transphenoidal hypophysectomy. Anesthetic management, preparation and monitoring were as in the first group. Following the first intravenous injection of *d*Tc, 0.3 mg/kg, CSF samples were obtained 15, 30, 60 and 90 minutes later. Immediately following the 90-minute sample, another injection of *d*Tc, 0.3 mg/kg, was given, and CSF samples were taken at similar intervals. Then a third injection of *d*Tc was administered and sampling of CSF continued for another 90 minutes. The second study covered a period of four and a half hours.

Serum was separated one to two hours after the sample was obtained and frozen until analyzed. CSF was frozen immediately. All samples were

analyzed by the radioimmunoassay method of Horowitz and Spector.⁸

Results

Small quantities of *d*Tc, $3.8 \pm .26$ ng/ml (mean \pm SE), appeared in the CSF within 5 minutes after a single intravenous injection of *d*Tc (fig. 1). There was no appreciable change in the 10-, 15-, or 20-minute samples. In the 30-minute sample, however, the concentration of *d*Tc increased to 9.3 ± 4.4 ng/ml. An hour after injection, the *d*Tc concentration in the CSF was 14.5 ± 4.5 ng/ml, and at one and a half hours, 17.1 ± 5.3 ng/ml. Over the remaining course of the study there was an irregular but overall increase in the CSF *d*Tc concentrations, which reached 24.9 ± 6.5 ng/ml six hours following injection.

The serum concentration of *d*Tc 5 minutes after a single intravenous injection was $3.05 \pm .13$ μ g/ml. Serum *d*Tc concentrations decreased along the usual exponential curve, declining to $0.733 \pm .086$ μ g/ml after one hour and $0.171 \pm .026$ μ g/ml after six hours.

There was considerable individual variation in the concentrations of *d*Tc in CSF (fig. 2). In six pa-

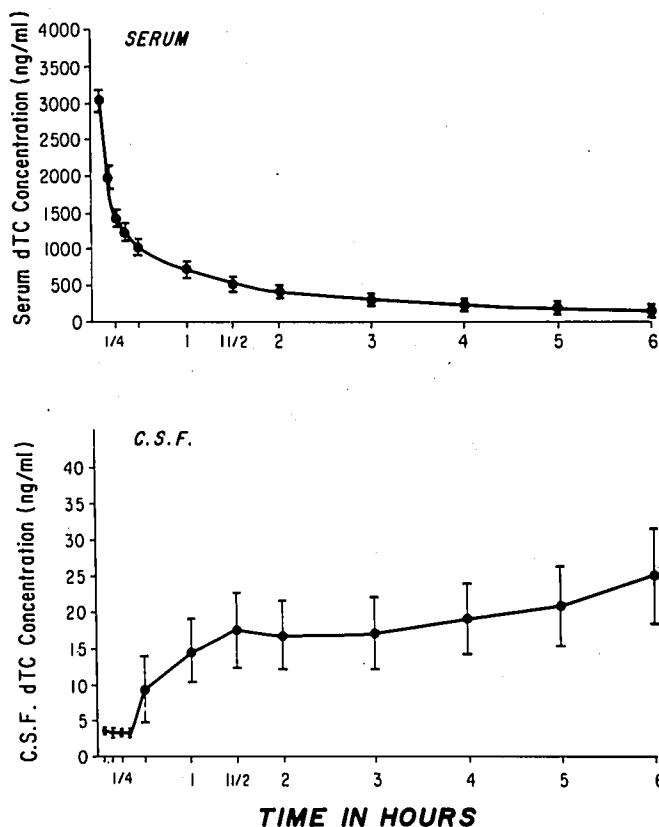


FIG. 1. Patients ($n = 9$) received a single injection of *d*Tc, 0.3 mg/kg, iv. Upper graph represents concentration of *d*Tc in the serum (mean \pm SE). Lower graph shows the concentration of *d*Tc in the CSF (mean \pm SE).

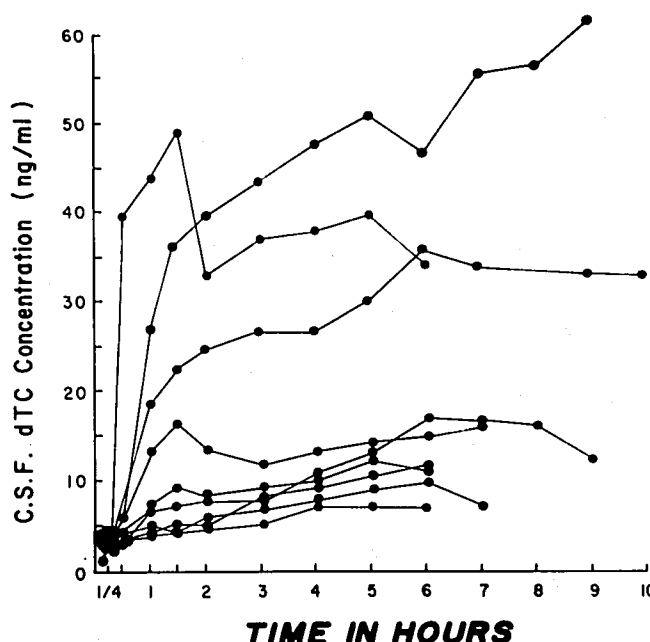


FIG. 2. Individual CSF *d*Tc levels in the nine patients who received a single injection of *d*Tc, 0.3 mg/kg, iv.

tients the CSF concentrations were similar, but in three patients concentrations of *d*Tc in the CSF were markedly higher. The patient with the highest concentration, 63 ng/ml at nine hours, had an arteriovenous malformation abutting on the third ventricle. The other two patients had pituitary tumors. All patients had serum electrolytes within normal limits.

When repeated doses of *d*Tc were administered, the concentration of *d*Tc in the CSF increased after each intravenous injection (fig. 3). The final CSF concentrations 90 minutes after the third intravenous injection of *d*Tc averaged 17.2 ± 2.6 ng/ml.

Discussion

We have found that *d*Tc can be detected in the CSF of man soon after its intravenous injection. The rapid appearance of *d*Tc in the lumbar spinal fluid is probably the result of diffusion of *d*Tc from the blood vessels supplying the spinal cord into the CSF. Five minutes after injection the mean concentration of *d*Tc in serum was $3.05 \pm .13$ μ g/ml, compared with 3.5 ng/ml in the CSF, a gradient of almost one to a thousand. After this immediate increase, the CSF concentration of *d*Tc did not change for more than 20 minutes. This suggests that a very high blood-CSF gradient is necessary for *d*Tc to diffuse directly into the CSF. The increase in CSF *d*Tc seen between 30 and 60 minutes and continuing in one patient for at least nine hours is probably the result of movement of CSF containing *d*Tc from the area of the choroid plexus to the lumbar subarachnoid space. A study

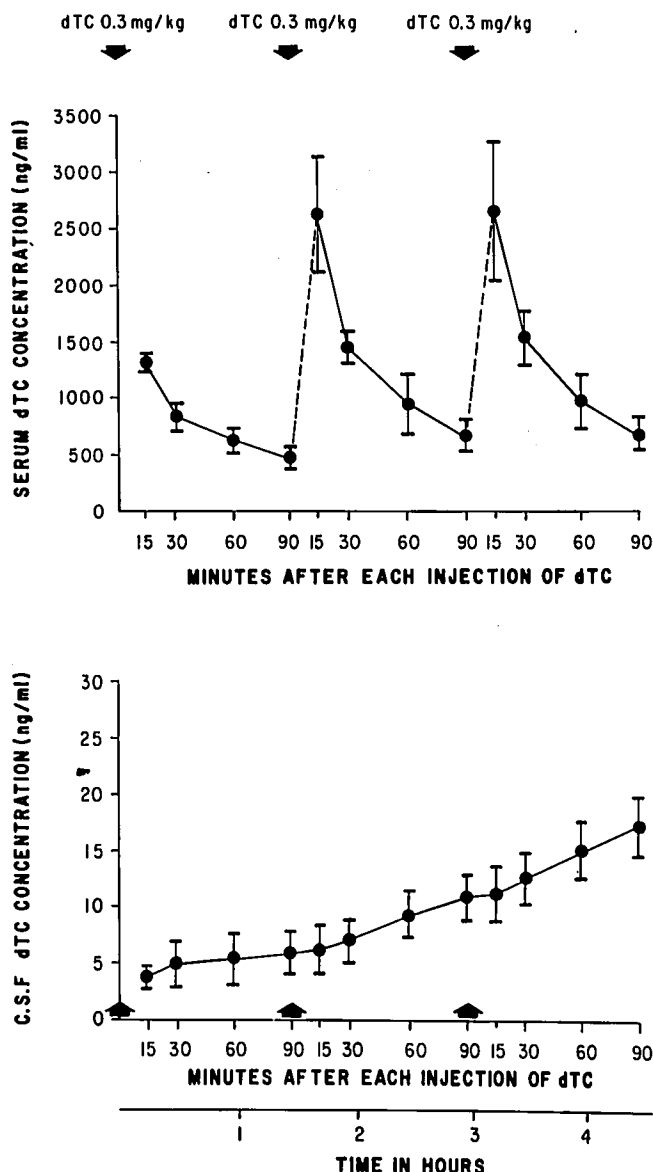


FIG. 3. Patients ($n = 6$) received three injections of dTc 0.3 mg/kg, iv, at 90-minute intervals. Upper graph represents the concentration of dTc in the serum (mean \pm SE). Lower graph shows the concentration of dTc in the CSF (mean \pm SE).

of the CSF distribution in man of another drug, methotrexate, demonstrated that methotrexate appeared in lumbar CSF within an hour of intraventricular injection.⁹ This delay approximates our findings with dTc .

The concentrations of dTc in CSF were generally lower after any interval when multiple intravenous doses of dTc were administered, compared with a single dose. The most likely explanation for this is that there is probably considerable variability among patients in the transfer of dTc from blood

to CSF, depending upon the underlying disease state, cerebral blood flow, etc.

A question arises as to how the removal of the CSF specimens may have affected CSF dynamics and concentrations of dTc in the patients' ventricles. We have no direct data to answer this question. Each sample involved the removal of approximately 1.5 to 2.0 ml of CSF (1.0 ml to clear the catheter deadspace; 0.5–1.0 ml for the sample). In the first group of patients this would involve removal of about 12 per cent of the CSF over a 90-minute period. In the second group, about half as much CSF was removed in the same period. Despite the twofold difference in volumes of CSF removed, the two groups showed the same general pattern of dTc recovery via the lumbar catheter (figs. 1 and 3—the rapid appearance, within 5 minutes, of the drug in the CSF, and a steady increase in concentration 15–30 minutes after injection. These indirect observations suggest that the sampling of CSF had little effect on the distribution of dTc in the CSF. Further, CSF in man is renewed approximately five and a half times each day.¹⁰ The quantities of CSF removed for sampling thus represent a very small fraction of the daily production of CSF.

The results of this study differ from those of Cohen, who could not detect dTc in the CSF of three patients following a single intravenous injection (0.3 to 0.6 mg/kg) of the drug.¹¹ We believe this difference can be explained by the sensitivities of the analytic methods employed. The radioimmunoassay for dTc is approximately 100 times more sensitive than the spectrofluorometric method available to Cohen when his study was done.

Although this study demonstrates that d -tubocurarine does penetrate the blood-brain barrier and can be detected in the cerebrospinal fluid, the concentrations are small, in the nanogram range. The highest concentration we observed was 60 ng, in a patient who had abnormal cerebral circulation, i.e., an arteriovenous malformation abutting on the third ventricle. In cats, Feldberg and Sherwood had to inject a minimum of 30 μ g into the lateral ventricles to produce symptoms that ranged from motor excitability to frank convulsions.³ All the animals survived. This suggests that the quantities of d -tubocurarine we found in the cerebrospinal fluid are unlikely to produce any pharmacologic or adverse effect in man.

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