Effects of d-Tubocurarine on Intracranial Pressure and Thalamic Electrical Impedance

Leena Tarkkanen, M.D.,* L. Laitinen, M.D.,† G. Johansson, M.D.‡

Immediate effects of intravenous injection of d-tubocurarine on intracranial pressure and thalamic electrical impedance were studied in neurosurgical patients. Arterial blood pressure and heart rate were recorded simultaneously. After an initial dose of d-tubocurarine (0.6 ± 0.1 mg/kg), average thalamic baseline impedance decreased by 1.3 per cent for 1–2 min and its pulse amplitude increased by 50 per cent. Simultaneously, average ventricular CSF pressure rose from 10.1 to 19.2 mm Hg. After a second dose (0.2 ± 0.1 mg/kg) the cerebral changes were smaller. d-Tubocurarine also decreased blood pressure and increased heart rate. The causes of the changes in thalamic impedance and in intracranial pressure are not known, but they probably result from increased pulsatile blood flow in the brain. (Key words: Neuromuscular relaxants: d-tubocurarine; Cerebrospinal fluid: pressure: d-tubocurarine; Brain: thalamus: impedance.)

The effects of d-tubocurarine on the peripheral circulation have been studied extensively.1–5 Its effects on intracranial conditions, on the other hand, are almost unknown. A few studies6 indicate that after peripheral administration it has a direct effect on the central nervous system. It seems probable, however, that under normal conditions it does not pass the blood–brain barrier to any great extent.7–10 So far as we know, its effect on intracranial pressure has not been assessed.

Recently, in connection with stereotaxic operations in man, we had an opportunity to study the effects of d-tubocurarine on intracranial pressure and cerebral electrical impedance. It had previously been determined that changes in intracerebral impedance reflect changes in regional blood flow.11

Methods

Twelve patients were studied in connection with 23 stereotaxic interventions. Except for one 54-year-old man, the patients' ages ranged from 12 to 24 years (mean 17 years). The indications for stereotaxic procedures were cerebral palsy in four patients, progressive myoclonus epilepsy in five, and chronic brain injury in three.

The patients were premedicated with atropine sulfate, and anesthesia was induced with sodium thiopental. Succinylcholine was used to facilitate endotracheal intubation. Anesthesia was maintained with 70–75 per cent nitrous oxide. Some adult patients received meperidine after induction. The patients were then allowed to breathe spontaneously for 1–2 hours, depending upon the time needed for insertion of electrodes. During this time normocapnia was achieved and the level of anesthesia stabilized.

Thereafter, d-tubocurarine chloride (Tubocurarin, Orion), 0.6 ± 0.1 mg/kg, was given iv. The effects of this first dose were studied in 20 tests. After d-tubocurarine administration the patients were allowed to breathe spontaneously for 1–2 min. Breathing was then assisted by hand until mechanical assistance by respirator was begun.

In 13 tests a second dose of d-tubocurarine (0.2 ± 0.1 mg/kg) was given 30–40 min later, while respiration was still being mechanically controlled. At that time respiratory volume and rate were unchanged during normocapnia.

In five sessions the procedures were performed on semiconscious tracheostomized patients during use of local anesthesia. The patients had received d-tubocurarine like the others and were connected to a respirator and ventilated with air.

Arterial pressure and ventricular CSF pressure were measured continuously with appropriate transducers through indwelling catheters placed in the femoral artery and the lateral cerebral ventricle, respectively. In-
D-TUBOCURARINE (0.7 mg/kg)

Fig. 1. Effects of an initial dose of d-tubocurarine (0.7 mg/kg) in a patient receiving anesthesia with N2O-O2.

### TABLE 1. Effects of Initial Dose of d-Tubocurarine (0.6±0.1 mg/kg) in 20 Spontaneously-breathing Patients*

<table>
<thead>
<tr>
<th></th>
<th>Before d-Tubocurarine</th>
<th>After d-Tubocurarine</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>132.3 ± 22.1</td>
<td>95.3 ± 26.2</td>
<td>-37.0±14.0 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78.5 ± 18.5</td>
<td>110.0 ± 25.4</td>
<td>+31.5±21.4 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Ventricular CSF pressure (mm Hg)</td>
<td>10.1 ± 4.1</td>
<td>18.2 ± 8.7</td>
<td>+ 8.1± 6.8 (P &lt; 0.001)</td>
</tr>
<tr>
<td>PacO2 (mm Hg)</td>
<td>39.1 ± 4.6</td>
<td>-43.7 ± 5.2</td>
<td>+ 4.6± 3.7 (P &lt; 0.05)</td>
</tr>
<tr>
<td>Thalamic impedance baseline (ohms)</td>
<td>1637 ± 610</td>
<td>1612 ± 606</td>
<td>-25 ±25.3 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Impedance pulse amplitude (per cent of baseline value)</td>
<td>0.4 ± 0.3</td>
<td>0.6 ± 0.5</td>
<td>+ 0.2± 0.4 (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

* Values immediately before and 60 sec after intravenous administration are given. Statistics: t test for correlated groups.
FIG. 2. Effects of a second dose of d-tubocurarine (0.4 mg/kg) on blood pressure, ventricular CSF pressure, and thalamic impedance in a patient. The unconscious patient had received an initial dose of 0.5 mg/kg d-tubocurarine 20 min earlier. Respiration was controlled by a respirator at constant rate and volume. Local anesthesia was being used.

<table>
<thead>
<tr>
<th>Table 2. Effects of Second Dose of d-Tubocurarine (0.2 ± 0.1 mg/kg) in 13 Patients during Respirator-assisted Respiration*</th>
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</thead>
<tbody>
<tr>
<td>Before d-Tubocurarine</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Ventricular CSF pressure (mm Hg)</td>
</tr>
</tbody>
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Thoracic pressure was measured with an air-filled balloon in the esophagus connected to the pressure transducer. All pressures were recorded on a three-channel polygraph (Mingograf 81B). Heart rate was calculated from the continuously recorded electrocardiogram.

Intracerebral impedance in the thalamus was measured by the monopolar technique described by Laitinen et al. and Tarkkanen. An impedance bridge (GR 1605-A) was connected to a one-channel DC recorder (Electronik 19, Honeywell). In seven tests the impedance electrode was introduced stereotaxically into the thalamus immediately before measurement of impedance was started. In 16 tests impedance was measured through an electrode chronically implanted in the target area weeks earlier.

Analyses of blood for arterial acid-base status and P02 were performed by the micro-Astrup technique. The steady state of normocapnia was checked by taking blood samples at least twice before d-tubocurarine administration, and in most tests again immediately after the beginning of manual assistance of respiration, i.e., 1–2 min after d-tubocurarine administration. End-expiratory CO2 analyses were performed with an infrared analyzer as a continuous check on P3CO2.

Results

Effects of the Initial Dose of d-Tubocurarine

The immediate changes in electrical impedance of the thalamus, ventricular CSF pressure, systolic arterial pressure, heart rate, and
Paco₂ after administration of the first dose of d-tubocurarine are presented in table 1 and figure 1.

The dominant changes were: ventricular CSF pressure rose, and simultaneously there was a drop in the impedance baseline and an increase in impedance pulsation. This increase averaged 50 per cent of the initial amplitude. When respiratory assistance was begun 1–2 min later, the direction of these changes was reversed. Arterial pressure fell and heart rate increased for a longer period (the maximum change was achieved within 1–3 min). Immediately after administration of d-tubocurarine there was often a transient rise in blood pressure (fig. 1) and a transient period (about 30 sec) of hyperventilation which caused irregular oscillations of intrathoracic pressure. Paco₂ rose slightly but remained within normal limits. Paco₂ did not change during these tests.

**Effects of the Second Dose of d-Tubocurarine**

The effects of the second dose of d-tubocurarine are presented in table 2 and figure 2. Changes were minimal or absent. When observed, however, they were always in the same direction as the changes after the first dose of d-tubocurarine. Ventricular CSF pressures were recorded in six tests. In all instances CSF pressures rose slightly. The impedance changes were also in the same direction but smaller than those seen after the first dose of d-tubocurarine. Paco₂ and intrathoracic pressure did not change in these tests.

**Discussion**

In the present study, d-tubocurarine caused a fall in blood pressure, an increase in heart rate, and a rise in ventricular CSF pressure with a simultaneous decline in the baseline and increase in the pulsation of the electrical impedance of the thalamus. The changes were marked in spontaneously breathing patients after the large initial dose of d-tubocurarine. After the small second dose the changes were similar but less striking. At the time of the second dose the patients were normocapnic; respiration was mechanically controlled, with unchanged respiratory volumes and rates.

The hypotensive effect of d-tubocurarine, well documented by earlier investigators, was confirmed in the present study. A transient rise in blood pressure immediately after intravenous injection of d-tubocurarine was noted by Tammisto and Welling. We confirmed this observation (fig. 1). At the same time, there was a short period of hyperventilation and oscillations in intrathoracic pressure. Our observation that d-tubocurarine increased heart rate agrees with the results of Smith and Whitcher and Tammisto and Welling.

It has been suggested that intracranial pressure is decreased by muscle relaxants through a fall in central venous pressure when muscle tone is reduced. In our study, in contrast to such reports, we found a marked increase in ventricular CSF pressure after the initial dose of d-tubocurarine and a smaller increase after the second dose. Initially all patients had normal intracranial pressures. After the initial dose there was also a slight increase in Paco₂ and oscillations in intrathoracic pressure were observed. These may have influenced intracranial pressure. The increase in Paco₂ was very small, however, within the normocapnic range, and seems unlikely to have been the cause of the increased intracranial pressure when the initial pressure was normal. The same applies to the changes in intrathoracic pressure, which were transient, i.e., intrathoracic pressure began to fall within about 30 sec, while ventricular CSF pressure was still rising. After the second dose of d-tubocurarine CSF pressure increased, though neither Paco₂ nor intrathoracic pressure changed. Although d-tubocurarine has been reported not to change cerebral vascular resistance, we suppose that the rise in ventricular CSF pressure found in this study was caused by vasodilatation in the brain. The very marked increase in the amplitude of impedance pulsation supports the idea of increased pulsatile blood flow. Another factor that may lead to increased intracranial pressure is liberation of histamine, with resulting increase in capillary-wall permeability and outward passage of fluids from cerebral capillaries, which produces cerebral edema. The decrease in the impedance baseline may support this idea, but can also be explained by assuming an increase in cerebral blood volume.
The patients in this study had normal intracranial pressures initially. It is likely that in patients with intracranial hypertension the effect of \(d\)-tubocurarine on the CSF pressure would have been still greater\(^2\) and of clinical importance. Until this aspect has been studied, it is advisable to administer \(d\)-tubocurarine slowly to patients with space-occupying lesions, beginning respiratory assistance immediately and hyperventilating the patients to achieve vasoconstriction in the brain.

References