STUDIES OF D-TUBOCURARINE WITH MEASUREMENTS OF CONCENTRATION IN HUMAN BLOOD

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The clinical use of muscle relaxants has increased many fold during the past decade and marks one of the great advances in the field of anesthesiology. None the less, their increased use has not been without serious problem. Beecher and Todd (1) report a six-fold increase in death rate when muscle relaxants are added to the anesthetic agents already employed. Other authors report complications of broncho-constriction (2, 3), hypotension (4, 5), and prolonged apnea (6) following the use of these substances. At the same time there exists a paucity of experimental studies both on the action and of the fate of these compounds in the body. A recent article by Foldes (7) on the fate of muscle relaxants in the human body points out the many "blind spots" caused by lack of adequate experimental data. Undoubtedly one of the most serious drawbacks to experimental study has been the lack of simple analytic techniques for the measurement of these substances. With the recent development of an accurate method for the spectrophotometric determination of d-tubocurarine in the plasma (8), the opportunity for further study has been made possible.

The following data represents a study carried out on 7 unanesthetized volunteers given large intravenous injections of d-tubocurarine. All studies were carried out in the fasting unpremedicated state. Each subject was able to serve as his own control in the course of repeated experiments.

Procedure.—Each subject was given a single rapid intravenous injection of aqueous d-tubocurarine, 0.1 mg. per pound of body weight. In different individuals this represented 15.5 to 24 mg. of d-tubocurarine hydrochloride. All subjects lay recumbent during the study period and were given manual artificial respiration (100 per cent oxygen) with bag and mask until the individual no longer required breathing assistance. Indwelling arterial and venous needles permitted sampling of blood as needed. Measurements of tidal volume and vital capacity were made with the aid of a Bennett ventilation meter. Direct measurements of biceps muscle contraction were made by a specially constructed spring pull scale. Recordings of blood pressure, pulse, and respiratory rate were made, and intercostal motion and diaphragmatic

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function were observed. Electrocardiographic studies were carried out on two subjects. All blood samples when possible were analyzed in duplicate measurement by the previously mentioned ultraviolet spectrophotometric technique. Control blood analyses were made on preliminary samples in each study.

_Blood Curare Levels._—Following the rapid intravenous injection of 0.1 mg. _d_-tubocurarine per pound of body weight, blood samples were drawn at prearranged intervals from cannulas in the opposite antecubital vein or radial artery. The levels of _d_-tubocurarine measured in 5 subjects and the disappearance of the drug from the blood plasma with the passage of time may be seen in figure 1. It will be noted that at the end of one minute most of the injected curare can be recovered from the blood plasma (calculated on the basis of plasma volume equals 5 per cent of body weight). Redistribution of the drug quickly follows. By the end of ten minutes, less than 60 per cent and by the end of twenty minutes, less than 40 per cent of the injected curare can be recovered from the blood plasma. This early redistribution phase is followed by a slower period of disappearance of the curare with approximately 25 per cent of the drug still remaining at the end of one hour. Elimination through the kidneys (9, 10) and destruction within the body continues, until at the end of three hours only traces of the drug are to be found in the plasma (subject E).
The observation that approximately 25 per cent of the intravenously injected dose of curare is still to be recovered from the plasma at the end of one hour's time is of extreme clinical importance. While it has been realized that a second smaller dose of curare repeated within an hour's time will produce the same degree of muscular paralysis originally produced by a larger dose, this residual curare carries a further hidden danger to the patient. During this period the postoperative patient remains susceptible to the respiratory depressant action of added narcotic drugs given for pain relief. This additive action of

![Graph showing distribution of curare between arterial and venous phases](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931675/)

**Fig. 2.** Distribution of curare between the arterial and venous phases following the intravenous injection of 0.1 mg. d-tubocurarine per pound of body weight. (Each dot represents the mean of 4 subjects.)

residual curare plus depressant narcotic drugs may at times be sufficient to throw the patient into severe respiratory depression. This is further discussed in the following section.

Figure 2 presents a composite graph of 4 subjects showing distribution ratios between the arterial and venous blood phases. It will be noted that these phases equilibrate within twenty minutes.

Vital Capacity and Plasma Curare Concentration.—Following the intravenous injection of 0.1 mg. d-tubocurarine per pound of body weight, measurements were made, at intervals, of vital capacity in each subject. Since the concentrations of curare used produced severe respiratory depression in all subjects, manual artificial respiration with oxygen was provided between testings. With the aid of the Ben-
nett ventilation meter connected to the customary anesthesia equipment, it was possible to assist the subject with his breathing as needed and yet obtain a direct minute to minute measurement of his vital capacity. As we observe in figure 3, very close correlation was found to exist between measured vital capacity and plasma concentrations of curare. It will also be noted that plasma concentrations of curare in excess of 4 γ per cc. produce almost complete respiratory embarrassment, but that respiratory function is back to normal with plasma levels of 1 γ per cc. still remaining. As will be recalled from figure 1, this concentration of the drug in the plasma is still present one hour following the original intravenous injection of 0.1 mg. d-tubocurarine per pound of body weight. It is this residual curare still present in the blood at the termination of surgical anesthesia that marks one of the dangers in the use of this substance. With plasma curare concentrations at 1 γ per cc. the individual’s respiratory ability is apparently normal (figure 3), but he remains dangerously sensitized to any additive effects from respiratory depressant drugs given for postoperative pain relief. Such added medicaments as morphine, meperidine (Demerol®), or Levo-Dromoran®, may force the patient into a state of severe respiratory depression. It has been our experience that the use of postoperative narcotics must be restricted in amount (one-half dosage) for at least three hours following the administration of curare for anesthetic use. Following shorter operations and anesthetic pro-

![Figure 3. Relationship between vital capacity and plasma curare concentration.](image-url)
procedures, one must also bear in mind the still present residual effects of narcotics used for preanesthetic medication. Some other disadvantages to the "routine" use of narcotics for preanesthetic medication have already been discussed elsewhere (11).

Measurements of Response by Individual Muscle Groups.—The difference in susceptibility of specific muscle groups to the blocking action of curare has been well established and provides the clinical basis for our use of this substance. Its respiratory saving action is undoubtedly the most essential characteristic. None the less, one frequently ob-

![Graph showing vital capacity vs. time](image)

**Fig. 4.** Measurements of vital capacity following the intravenous injection of 0.1 mg. \(d\)-tubocurarine per pound of body weight.

serves in the individual patient variations in types of skeletal muscle response. In some individuals there appears clinically to be little range between that concentration of curare which produces respiratory paralysis and that producing abdominal muscle relaxation sufficient for surgery. In other individuals, we observe, voluntary movements of the neck or of the extremities in the presence of sufficient curarization for extreme respiratory weakness and complete abdominal wall relaxation.

In a series of 5 individuals we attempted to time the return of intercostal muscle activity following the injection of 0.1 mg. \(d\)-tubocurarine per pound of body weight. It was found that there was a variation both in the time and in the concentration of plasma curare at which this occurred. The range in timing was 16 to 25 minutes following the
original curare injection, and the plasma concentrations of curare at
the first return of intercostal activity varied from 1.6 to 2.9 \gamma per cc.

In these same 5 individuals we employed an apparatus constructed
to measure muscle pull against a fixed weight scale. Measurements of
biceps muscle pull were determined at various times and appropriate
blood samples were drawn and analyzed for curare content. The re-
ponses varied considerably showing little correlation between plasma
concentrations of curare and loss of biceps muscle strength.

It is our feeling that the responses of individual muscle groups pro-
vides a poor index of general curarization of the patient. There exists
a wide latitude of response. On the other hand, there is a good correla-
tion between the general reduction of respiratory ability measured by
vital capacity and plasma concentrations of curare (figure 3). In

| TABLE 1 |
|---|---|
| Cardiovascular Effects Following the Intravenous Injection of |
| 0.1 Mg. d-Tubocurarine Per Pound of Body Weight |

<table>
<thead>
<tr>
<th>Group I</th>
<th>Blood Pressure</th>
<th>Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Curare injection</td>
<td>158/78*</td>
<td>114</td>
</tr>
<tr>
<td>Peak effect</td>
<td>132/80</td>
<td>134</td>
</tr>
<tr>
<td>Post-Curare</td>
<td>134/74</td>
<td>84</td>
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<tr>
<td>(−16%)</td>
<td>(+18%)</td>
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</table>

<table>
<thead>
<tr>
<th>Group II</th>
<th>Blood Pressure</th>
<th>Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Curare injection</td>
<td>136/66</td>
<td>90</td>
</tr>
<tr>
<td>Peak effect</td>
<td>128/70</td>
<td>101</td>
</tr>
<tr>
<td>Post-Curare</td>
<td>114/68</td>
<td>82</td>
</tr>
<tr>
<td>(−6%)</td>
<td>(+12%)</td>
<td></td>
</tr>
</tbody>
</table>

* Each figure represents the arithmetic mean of all subjects studied.

figure 4 is demonstrated the reduction of normal vital capacity follow-
ing the intravenous injection of curare and its gradual return to normal
at the end of 60 minutes.

Cardiovascular Effects of Curare.—Various experimental (4, 5)
and clinical reports have suggested a hypotensive action following the
intravenous injection of large doses of curare. We were unable to
demonstrate this action in any of our subjects. This difference in re-
sponse could be accounted for by the fact that in this study we were
able to completely separate the cardiovascular effects of curare from
those of other concomitantly administered drugs. Furthermore, our
subjects were young and healthy volunteers, unpremedicated, unanes-
thesitized, and not subjected to traumatic surgical interference. The
cardiovascular effects of curare were studied in 5 individuals, each of
whom participated in two identical experiments. Group I represents
the first combined study of these 5 individuals, and group II the same
study at a later date. Reference to table 1 shows the lessened effects of
fear and anticipation between group I and group II. We note the lower
pre-experimental recordings of blood pressure and pulse in group II.
It will be noted from table 1 that the mean drop in blood pressure was
only 6 per cent in group II, and that the increase in pulse rate was 12 per cent. These effects are very negligible and undoubtedly would be lessened still further in trained subjects.

Electrocardiographic tracings were prepared in two of the above studied subjects. No significant changes were noted in these tracings.

*Anticurare Compounds.*—The antagonism of curare by both neo-stigmine (12) and by edrophonium (13) has been thoroughly established. It is postulated that neostigmine exerts essentially an anticholinesterase action. Edrophonium exerts some anticholinesterase activity, but in addition has a direct effect on the motor end plate itself. The relative contribution of these two components to the anticurare action of edrophonium has not yet been established (14).

Several experiments were carried out in order to study and compare the actions of the above mentioned anticurare compounds. Following the intravenous injection of 0.1 mg. *d*-tubocurarine per pound of body weight and at the peak depressant effect, injections of the various anticurare compounds were made. The release of the curare effect was measured in terms of change in vital capacity and by direct measurements of plasma curare concentrations. By utilizing the same subjects in a series of experiments each individual was able to serve as his own control.
In figure 5 we observe the antcurare action of edrophonium (Tensilon®). As can be seen the plasma level of curare markedly decreased following the injection of a therapeutic dose of edrophonium. This depression lasted approximately ten minutes, then the plasma concentration of curare returned to control levels. From this point on it paralleled the control study, both gradually falling off with the passage of time. Reference to simultaneous measurement of vital capacity in both the edrophonium and control studies show close correlation to plasma curare levels. This experiment further emphasizes the fleeting action of edrophonium as compared to the longer action of \(d\)-tubocurarine. This is of significant clinical importance when the patient who has had an antidotal dose of edrophonium becomes curarized again within a relatively short time (ten minutes). Under these circumstances the dose of edrophonium must be repeated once or twice again as necessary until the concentration of curare in the plasma has been permanently diminished.

In figure 6 may be seen a series of experiments studying the antcurare action of neostigmine. It will be noted that neostigmine has a depressant effect on plasma levels of curare similar to that of edrophonium. We also noted the correlation in measurements of vital capacity. As in figure 5, these closely parallel plasma curare concen-
trations. While the curare antidotal effect of neostigmine is both slower and less marked than that of edrophonium, its duration of action was considerably longer and can be seen to have outlasted the twenty-minute study period of the experiment.

The lack of further experimental data permits only speculation as to the mechanism by which neostigmine and edrophonium depress plasma curare concentrations. One may theorize the possible formation of a loosely bound curare-anticurare molecule. More likely we must consider the mechanism of temporary redistribution of the curare itself within other body tissues. Certainly we must seek more explanation to account for the antidotal effects than mere increases in anticholinesterase activity. Our studies are being continued on tissue redistribution, and we hope that this work will provide answers to some of these questions.

**Summary**

The elimination of curare by the body with the passage of time was studied in a series of subjects following a single intravenous injection of 0.1 mg. d-tubocurarine per pound of body weight. It was found that at the end of one hour approximately 25 per cent of the originally injected curare was still present in the plasma, although the subject's respiratory ability had apparently returned to normal. The clinical importance of this finding is discussed.

A study of the respiratory, hemodynamic, and muscular actions of d-tubocurarine was made on a series of unanesthetized subjects. Plasma levels of curare were measured and correlated with the above studies. Close correlation was observed between plasma concentrations of curare and reduction of vital capacity. However, considerable variation was found in measurements of plasma curare concentration and return of intercostal activity or in strength of the biceps muscle. We were unable to demonstrate any significant hemodynamic changes following the intravenous injection of curare in the unanesthetized subject.

The action of anticholinergic compounds on the plasma levels of curare was also studied and correlated with measurements of vital capacity. It was observed that both edrophonium and neostigmine produce a reduction in plasma curare concentration and a concomitant improvement in measured vital capacity. The action of the former compound (edrophonium) is outlasted by the residual curare effects.

**REFERENCES**


