

A QUANTITATIVE STUDY OF *d*-TUBOCURARINE IN MAN DURING DIETHYL ETHER ANALGESIA

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FOLLOWING our description of ether analgesia¹ in 1955, we have used the technique regularly in this institution in association with muscle relaxants for abdominal surgery. Therefore, we believed it appropriate at this time to determine the dose-response relationship of *d*-tubocurarine during analgesia in man and to compare the results with the dose-response curves of *d*-tubocurarine during conventional surgical anesthesia, the latter having been studied earlier by this department.²

METHOD

These studies were performed on 19 patients ranging in age from 16 years to 57 years and in weight from 50 to 89 kg. All subjects were anesthetized with diethyl ether to the analgesic level as described by Artusio.¹ Respiratory minute volume (RMV) and expiratory tidal volume were measured, and their changes served as indicators of the degree of curarization. This method was previously described by Artusio, Riker, and Wescoe.³ The subjects were maintained in the analgesic stage using the EEG as an objective criterion of central nervous system depression. Unilateral frontoparietal leads were monitored and the predominant 24 cycle per second pattern described by Bellville and Artusio was maintained.⁴

After control observations were recorded, curare was administered. In accordance with the degree of changes produced by curare, the patients were grouped into three categories: Group A were those patients whose RMV was reduced to 40–60 per cent of control values. Group B were reduced to 20–40 per cent of control RMV; and group C to 0–20 per cent of control RMV.

Repeated doses of relaxants were given to

patients in each group to study summation of effects.

All patients had undergone elective surgery and were judged preoperatively to be free of clinical or laboratory evidence of cardiac, pulmonary, hematologic, renal, or neurologic disease. The studies for the most part were performed in a separate room following the termination of the surgical procedure. When the respiratory exchange was believed to be inadequate, respiration was assisted at intervals to prevent hypoxia and accumulation of carbon dioxide. Blood pressure (sphygmomanometric), cardiac rate, and rhythm were obtained by auscultation at the brachial artery and were recorded simultaneously with the RMV.

RESULTS

GROUP A. (FIG. 1): *Intensity of Action.* The initial dose of *d*-tubocurarine reduced the RMV to 54 per cent of control while the second and third equal doses further reduced the RMV to 29 and 21 per cent respectively of control values, as shown in figure 1.

Duration of Action. Those patients curarized by an initial dose to between 40–60 per cent of control RMV recovered in a predictable manner in an average of 29 minutes. Second and third dose recovery times were 52 minutes in both instances.

GROUP B. (FIG. 2): *Intensity of Action.* The initial dose of *d*-tubocurarine reduced the RMV to 30 per cent of control value while the second and third equal doses further reduced the RMV to 16 and 13 per cent of control values respectively, as shown in figure 2.

Duration of Action. Those patients curarized to between 20–40 per cent of control RMV also recovered in a predictable manner in an average of 22 minutes. Second and third dose recovery times were 46 and 56 minutes respectively.

Accepted for publication January 5, 1960. The authors are in the Department of Anesthesiology, The New York Hospital, and the Department of Surgery (Anesthesiology), Cornell University Medical College, New York 21, New York.

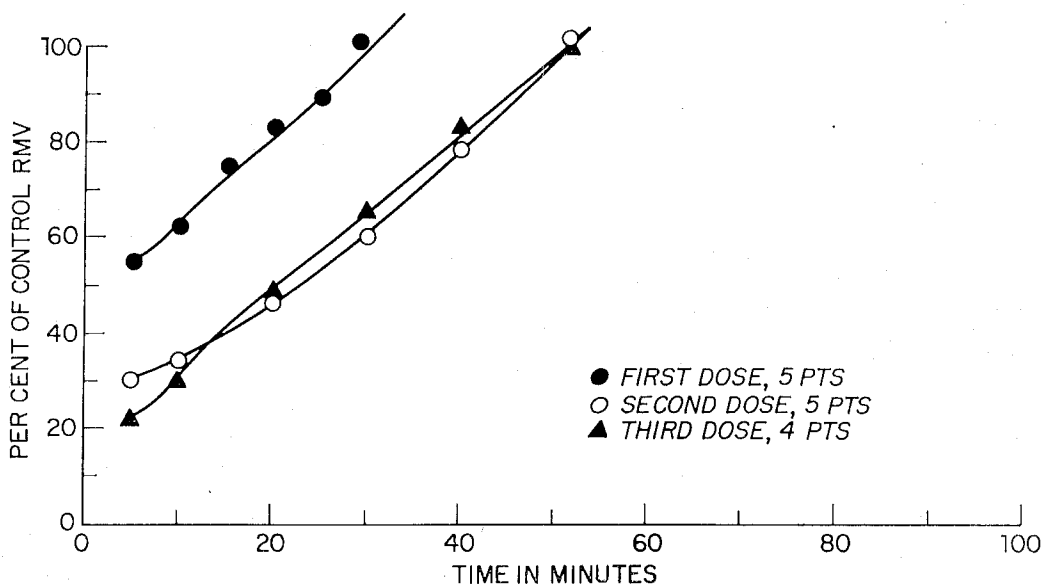


FIG. 1. *d*-Tubocurarine-ether analgesia. Effect of second and third equal doses of *d*-tubocurarine following initial depression of respiratory minute volume to 40-60 per cent by first dose.

GROUP C. (FIG. 3): *Intensity of Action.* The initial dose of *d*-tubocurarine reduced the RMV to 11 per cent of control RMV while the second and third equal doses further reduced the RMV to 4 and 1 per cent of control values respectively, as shown in figure 3.

Duration of Action. Those patients curarized to between 0-20 per cent of RMV recovered in an average of 28 minutes. Second and third dose recovery times were 54 and 90 minutes respectively.

AVERAGE MG./KG. RESPONSE: (TABLES 1

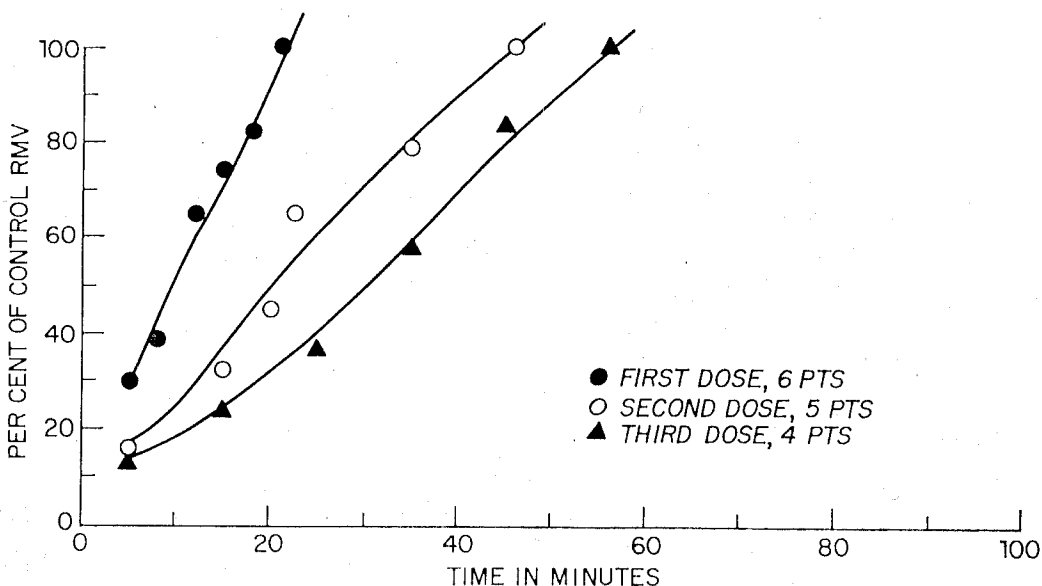


FIG. 2. *d*-Tubocurarine-ether analgesia. Effect of second and third equal doses of *d*-tubocurarine following initial depression of respiratory minute volume to 20-40 per cent by first dose.

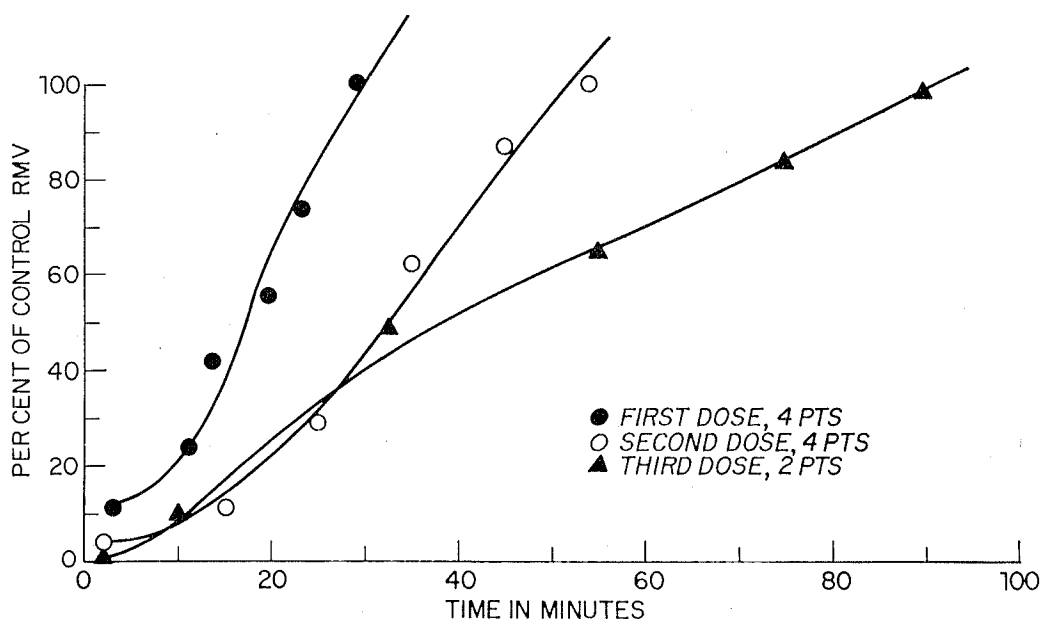


FIG. 3. *d*-Tubocurarine-ether analgesia. Effect of second and third equal doses following initial depression of respiratory minute volume to 0-20 per cent by first dose.

AND 2). Eight patients whose RMVs were depressed to an average of 30 per cent of control value received an average of 0.10 mg./kg. However, no relationship could be established between curare dose and curare effect in any single patient in this series. This average dose of 0.10 mg./kg. may be compared with the 0.11 mg./kg. average dose administered by Artusio, Marbury, and Crews

TABLE 1

DOSE RESPONSES OF EIGHT INDIVIDUAL PATIENTS TO *d*-TUBOCURARINE (MG./KG.) AT ANALGESIC LEVELS OF ETHER

Patient		Curare Dose (mg./kg.)	Level of Curarization Per Cent of Control RMV
Age	Sex		
44	♀	0.08	16
40	♀	0.12	18
31	♀	0.12	30
54	♂	0.07	30
19	♂	0.08	33
34	♀	0.11	33
57	♂	0.09	37
16	♂	0.12	40
Average		0.10	29.8

RMV = Respiratory minute volume.

TABLE 2

DOSE RESPONSES OF FIVE INDIVIDUAL PATIENTS TO *d*-TUBOCURARINE (MG./KG.) IN LIGHT SURGICAL ETHER ANESTHESIA

Patient		Curare Dose (mg./kg.)	Level of Curarization Per Cent of Control RMV
Age	Sex		
48	♂	0.14	38
38	♂	0.13	31
52	♂	0.08	31
57	♀	0.10	28
53	♂	0.11	22
Average		0.11	30

RMV = Respiratory minute volume.

in the presence of surgical ether anesthesia which produced a similar average depression of 30 per cent of control RMV.²

EFFECT ON VITAL SIGNS: During these experiments, pulse and respiratory rate did not change significantly in any patient. Blood pressure was stable except for insignificant and brief hypotensive episodes in several patients immediately following *d*-tubocurarine injection. The EEG configuration (low amplitude, 18-24 cycles per second) remained unchanged after injection of *d*-tubocurarine.

DISCUSSION

Recovery from an initial dose of curare averages 25 minutes during ether analgesia regardless of degree of depression produced by the relaxant (figs. 1, 2 and 3). This figure may be compared to the 40 minutes required for recovery during stage III, plane 1 ether, shown earlier by Artusio, Marbury and Crews.²

Recovery from a *second* equal dose of *d*-tubocurarine averages 50 minutes (figs. 1, 2 and 3). However, the duration of effect in all cases was significantly longer than the effect of the initial dose, indicating that during analgesia summation of effect was seen in all patients studied. If this result is compared with the data of Artusio, Marbury, and Crews,² it is shown that the duration of effect was decreased by almost 50 per cent from that seen during surgical anesthesia.

Recovery from a third equal dose depends on degree of initial depression and further summation of effect is seen.

It is apparent, therefore, that ether potentiates curare even at the analgesic level,⁵ although the *duration* of this effect is significantly reduced. That this is true is indicated by the finding (table 1) that the average intensity of effect of curare on a mg./kg. weight basis was approximately the same in this series of analgesic patients as in the earlier series wherein the patients were carried in light surgical ether anesthesia.² Ether apparently continues to "sensitize" the junctional region to *d*-tubocurarine even at minimal blood levels, although the relaxant appears not to be bound as tightly to receptor substance as it escapes more readily. This would account for the shorter duration.

However, the augmentation by ether in analgesic doses of respiratory depression from curare may be related to other factors than those presented here. For example, such factors as centrally-induced changes of discharge patterns from the respiratory center, or reduction during ether analgesia of afferent drive

of respiratory center could also contribute to the observed net effect. Thus, it must be understood that the conclusions drawn above are based on the technique used by us. Another technique—*e.g.*, the electromyogram—might produce different results.

SUMMARY

A series of patients maintained in the first stage of anesthesia using diethyl ether was given single intravenous injection of *d*-tubocurarine in order to obtain three distinct levels of depression of the respiratory minute volume (RMV). Recovery to control RMVs was observed. Subsequently, second and third equal doses of *d*-tubocurarine were administered to each of the groups of patients studied.

This study showed that the respiratory depression of *d*-tubocurarine was of the same intensity whether the patient was in stage I or stage III of diethyl ether anesthesia. However, the duration of action of the relaxant was much less in the lighter level. During the analgesic stage the effect of *d*-tubocurarine was 38 per cent shorter in duration for a first dose and 50 per cent shorter duration for a repetitive (second) dose of *d*-tubocurarine.

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