THE USE OF DECAMETHONIUM BROMIDE FOR THE PRODUCTION OF MUSCULAR RELAXATION

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Decamethonium salts have been made available recently to anesthesiologists and others interested in the use of curare-like drugs. These substances, originally synthesized in England, have been studied most extensively in that country (1, 2, 3, 4, 5, 6, 7, 8). It seems appropriate to present our results with decamethonium bromide + in 250 surgical patients for the following reasons: (a) this compound is now available in the United States; (b) it is freely miscible with pentothal; (c) it is cheap and stable, and (d) it does not liberate histamine from the body tissues. On the basis of our clinical experience we believe that the drug will be useful in anesthesiology and suggest its further investigation by other workers.

HISTORY

The decamethonium compounds represent a triumph of chemical planning and synthesis. d-tubocurarine chloride contains two quaternary nitrogen atoms and is much more powerful in blocking neuro-muscular transmission than are simple quaternary ammonium compounds. Barlow and Ing (1, 14) reasoned that curariform activity might be the result of the presence of two such groups at some optimal distance apart. They prepared and tested for curare-like action a number of simple compounds in which the quaternary nitrogen atoms were separated by straight carbon chains of varying lengths. The compound with a ten carbon chain proved to be the most potent, being about three times as active as d-tubocurarine chloride in producing head drop in the rabbit. This substance was known as C-10 initially and was available as a bromide or an iodide salt. The descriptive term "decamethonium" has since been adopted.

One important fact emerged from the original animal work reported on this series of compounds. Paton and Zaimis (2, 4) and Barlow and Ing (1) pointed out a significant species variation in response to the drug in the monkey, cat, rabbit, and rat. The degree and duration of paralysis varied considerably, as did the susceptibility of

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† Synseurine, Burroughs Wellcome and Company, Inc., brand Decamethonium bromide.
different muscles. At some dosage levels even an anticholinesterase response was observed at the nerve-muscle junction. As these workers emphasized, such results indicate the necessity for testing synthetic curare-like drugs on a variety of test objects before a final selection can be made.

The first trial of a decamethonium compound in man was reported by Organe, Paton, and Zaimis (3) in January 1949. Three milligrams of the iodide salt was injected intravenously into each of the investigators. The first subjective effect was on the eyes and eyelids, occurring within twenty seconds. Paralysis began in the eyelids, ocular muscles, and facial muscles and later affected the neck, trunk, and limbs. At the peak of the paralysis 2 of the subjects were unable to move their limbs or head; the third was less weakened. In all three, respiration was reported to have been unaffected although no data were given. Sensory perception was normal. Salivation was not bothersome. Recovery began in about ten minutes. These findings have been confirmed by Grob, Harvey, and Holaday (13).

**TABLE 1**

<table>
<thead>
<tr>
<th>Age: Range 12 to 85 Years</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-20</td>
<td>14</td>
</tr>
<tr>
<td>21-30</td>
<td>45</td>
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<tr>
<td>31-40</td>
<td>64</td>
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<tr>
<td>41-50</td>
<td>70</td>
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<tr>
<td>51-60</td>
<td>23</td>
</tr>
<tr>
<td>61-70</td>
<td>21</td>
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<td>Over 70</td>
<td>13</td>
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It was evident that decamethonium salts might be useful clinically for the production of muscular relaxation during anesthesia and in the prevention of muscular spasms during convulsive therapy. In May 1949, British workers reported successful results in surgical and psychiatric patients (5, 6, 7, 8).

**Methods**

Two hundred and fifty patients, 199 female and 51 male, were observed in this study. The majority of the group were between the ages of 31 and 50 years, with a range of 12 to 85 years (table 1). The average weight of the patients was 138 pounds with a range of 71 to 242 pounds.

The first 50 patients receiving decamethonium bromide were healthy, adult females scheduled for some type of gynecologic operation. The remaining patients were entirely unselected. Many were in poor physical condition because of hypertension, coronary disease, intestinal obstruction, diabetes, or other complicating factors. Practically all
types of operative procedures were carried out on these patients, the majority having had intra-abdominal operations (table 2).

All patients received preanesthetic medication of morphine and atropine or scopolamine in appropriate doses approximately one hour before the induction of anesthesia. Fifty patients in this series received a combination of pentothal and decamethonium bromide for induction of anesthesia and endotracheal intubation. The maintenance of anesthesia was then carried out with cyclopropane, nitrous oxide-oxygen and/or pentothal. The remaining 200 patients were anesthetized throughout with cyclopropane or ether or both. An attempt was made to keep the plane of anesthesia as light as possible and to obtain muscular relaxation with decamethonium bromide.

**TABLE 2**

**TYPES OF OPERATIONS**

1. Upper abdominal operations ........................................... 37
   Cholecystectomy ..................................................... 9
   Gastric resection .................................................. 13
   Intestinal resection ................................................. 5
   Splenectomy .......................................................... 2
   Upper abdominal exploration ....................................... 8

2. Lower abdominal operations ........................................... 160
   Gynecologic (supravaginal, total hysterectomy and salpingo-oophorectomy) ........................................... 122
   Appendectomy ......................................................... 13
   Intestinal resection ................................................ 8
   Colostomy ............................................................... 5
   Suprapubic prostatectomy ............................................ 5
   Exploratory laparotomy ............................................ 4
   Inguinal hernioplasty ............................................... 1
   Ligation of vena cava ............................................... 1
   Cesarean section ..................................................... 1

3. Miscellaneous .......................................................... 53

Total .............................................................. 250

Blood pressure, pulse and respiratory rate were recorded; observations were made on respiratory depth, pattern of respiration, degree of muscular relaxation and color of the skin. At the completion of the operation the patient was admitted to the post anesthetic observation room and observed until recovery from anesthesia had occurred. The course of the patients was followed for six to twelve days postoperatively and any complication recorded.

**RESULTS**

1. *Dosage.*—The initial dose of decamethonium bromide varied with the type of operation; 2 to 3 mg. for lower abdominal and 3 to 4 mg. for upper abdominal procedures were given as a rule. A combination of decamethonium bromide in 4 to 5 mg. and pentothal in 300 to 400 mg. doses was given for the purpose of rapid induction of anesthesia.
and prompt endotracheal intubation. The rate of injection was rapid, the entire amount being given in less than one minute. Although we observed no ill effects, we believe that two or three minutes for injection is preferable. It may be recalled that fatalities have been reported following the rapid administration of curare to apparently sensitive individuals (9).

Maintenance doses of 1 to 3 mg. of decamethonium bromide were given when additional relaxation was required. These doses were generally necessary only at times of abdominal exploration, packing away of the intestines or closure of the peritoneum so that it was not necessary to keep the patient continuously "curarized."

Total doses of decamethonium bromide varied with the type and duration of the operative procedure. An initial dose of 2 to 3 mg. for an appendectomy or suprapubic prostatectomy of twenty to thirty minutes duration was frequently all that was required. The largest total dose given was 20 mg. for a gastric resection that lasted 5 hours.

In a comparison of potency it can be stated that decamethonium bromide is about three times as potent, milligram for milligram, as d-tubocurarine chloride.

2. Duration of Action.—It is difficult to determine the time constants of a myoneural blocking agent unless one is recording action potentials from a muscle. Clinically, however, the following impressions were gained from observation of the effect of single doses of decamethonium bromide: the onset of action was rapid, reached a maximum within three or four minutes, began to wear off in eight to ten minutes and had completely disappeared in twenty to thirty minutes.

We are not able to answer satisfactorily the question of cumulative action. As will be noted subsequently, 4 patients were encountered who had prolonged apnea following the administration of large doses of decamethonium bromide. Their response was similar to that of patients to whom large doses of curare had been given.

3. Antagonism.—It has been shown that drugs inhibiting cholinesterase are of no value as antagonists for decamethonium bromide (2, 4). Pentamethonium bromide has been reported to be of some value as an antagonist (3, 4). We had none available and cannot confirm this finding. As respiratory depression was the only complication encountered we believe that adequate ventilation with oxygen is the most satisfactory treatment for overdosage.

4. Effects on Respiration.—Decamethonium bromide used in amounts sufficient to cause adequate relaxation of abdominal muscle caused definite respiratory depression. This depression was directly related to the size of the dose. Clinical estimation of decrease in respiratory depth following decamethonium bromide was as follows: mild with 2 mg., moderate with 3 mg., and severe with 4 mg. Apnea of four to ten minutes commonly followed doses of 4 or 5 mg. After
spontaneous respiration was resumed, return to normal depth of breathing was rapid, being complete in three to five minutes.

A most interesting response was the consistent increase in respiratory rate which followed doses of decamethonium bromide in the range of 1 to 2 mg. An increase in rate of 50 to 100 per cent occurred within two or three minutes and persisted for an additional five to ten minutes. This response was not correlated with marked depression of respiratory depth. The cause of this response remains obscure. Davies and Lewis reported similar results with d-tubocurarine (6).

The respiratory muscles were paralyzed in the same order as with curare, the action of the diaphragm and accessory muscles being the last to disappear.

Several patients have shown prolonged respiratory depression. The most notable example was a 53 year old man who received a total of 11 mg. of decamethonium bromide during a five-hour gastric resection, the last dose having been 1 mg., thirty minutes before completion of the operation. The patient had been on “controlled respiration” until after closure of the peritoneum, then spontaneous respirations were allowed to return. It was noted at this time that respiration was entirely diaphragmatic. At the end of the operation respiration had not improved and assisted respiration was necessary for the following forty-five minutes. Depth of breathing then began to increase rapidly and was entirely normal within fifteen minutes. Reflexes and consciousness returned and the patient had an uncomplicated postoperative course. Three other patients were judged to have somewhat prolonged respiratory depression.

5. Effects on Circulation.—In the amounts used in this study decamethonium bromide exerted no deleterious effects on the circulation. Even doses sufficient to cause complete muscular flaccidity and respiratory paralysis did not cause fall of blood pressure or significant change of pulse rate. Twenty-three patients with hypertension of 180 mm. systolic and 100 mm. diastolic or greater, several with a history of myocardial infarction and several with borderline congestive failure, received decamethonium bromide without ill effects.

Five unanesthetized subjects were given decamethonium bromide in 4 mg. doses over a period of three or four minutes. Ventilation with oxygen was carried out while intra-arterial blood pressure and electrocardiographic tracings were recorded. Again no significant circulatory effects were noted.

6. Abdominal Muscular Relaxation.—Clinical evaluation of muscular relaxation is difficult. In addition to drug action, the physical habitus of the patient, the type of operation, the respiratory pattern and the demands of the surgeon must be considered. Decamethonium bromide was judged to give fair to excellent relaxation in all but 2 patients. Depending upon the dose, any degree of muscular flaccidity could apparently be produced. We could detect no difference between
decamethonium bromide and d-tubocurarine chloride, as far as degree of relaxation was concerned, when the drugs were given in comparable doses.

7. Decamethonium Bromide-Pentothal Combination for Rapid Induction and Endotracheal Intubation.—This procedure was carried out in 50 patients as follows: 4 to 5 mg. of decamethonium bromide and 300 to 400 mg. of pentothal, either in separate syringes or in the same syringe, were injected rapidly over a period of fifteen to sixty seconds. As soon as the patient became unconscious a mask was applied and artificial ventilation with oxygen carried out for two or three minutes. We believed this to accomplish two things; it permitted time for the maximum effect of the drugs to occur and it afforded a safety factor in the form of increased pulmonary oxygen reserve. The endotracheal tube was then introduced under direct vision. This method was satisfactory and we gained the impression that the vocal cords were less irritable and cord spasm less common than when curare-pentothal combinations were used for similar purposes. As would be expected when using two respiratory depressant drugs, marked depression of respiration was commonly present following this procedure.

8. Use of Decamethonium Bromide with Various Anesthetic Agents.—We have used the drug with all of the commonly used inhalation agents except ethylene. The effects were additive, no instances of synergistic action having been found. Particularly encouraging was the fact that ethyl ether did not potentiate the action of decamethonium bromide.

9. Postoperative Course.—Decamethonium bromide did not appear to prolong the period of recovery from general anesthesia in the majority of cases. It must be admitted, however, that return of consciousness was delayed in the 4 patients who had prolonged respiratory depression. This suggests a depressant action on the central nervous system which deserves further study.

Data relating to gastrointestinal, urinary, and pulmonary complications were recorded for 224 patients as follows: vomiting one to two times, 54; vomiting three to four times, 40; over four times, 22, or a total of 116 patients or 52 per cent; nausea only 26 or 11 per cent, and no nausea or vomiting, 82 or 37 per cent. Urinary retention of some degree occurred in 28 (13 per cent) patients. Catheterization was performed one or two times in 22 patients, three or four times in 5 patients and over four times in one patient.

Two instances of atelectasis occurred, one following a gastric resection and one following pulmonary lobectomy. No cases of pneumonia were noted.

10. Release of Histamine.—Injection of curare has been shown to cause bronchoconstriction and a decrease of blood pressure in both animals and human beings (10, 11, 12). It has been suggested that these reactions are caused by the release of histamine from body tis-
sues. The intracutaneous and intra-arterial injection of d-tubocurarine chloride causes typical histamine reactions in the skin, (10, 12).

No instances of bronchoconstriction or sudden fall of blood pressure due to decamethonium bromide occurred in this series. The effect of intracutaneous injection of decamethonium bromide was studied on 9 volunteers. Decamethonium bromide (0.05 ml.), d-tubocurarine chloride and physiologic saline solution were injected intracutaneously at individual sites on the forearm. The sites of injection were examined and compared at one, five and fifteen minutes. d-Tubocurarine chloride caused typical wheal and flare formation in all 9 subjects. Slight flare formation occurred at the site of injection of decamethonium bromide in 5 of the subjects; none developed wheals.

**Discussion**

The principal difference of opinion among British anesthesiologists was whether a decamethonium salt could produce satisfactory muscular relaxation while sparing the muscles of respiration. Hewer, Lucas, Prescott and Rowbotham (7) stated that "relaxation comparable to that of d-tubocurarine could only be obtained with doses which paralyzed the muscles of respiration." Organe (5) noted that "in some cases the tone of the abdominal flank muscles persists as long as does respiration. In such cases it may, rarely,† be necessary to paralyze respiration before sufficient relaxation can be secured for peritoneal closure." Our experience was midway between these positions. For lower abdominal operations adequate working conditions could frequently be secured with block of only the lower intercostal muscles. During many upper abdominal procedures respiratory paralysis and "controlled respiration" were required for profound muscular relaxation. In our opinion this situation obtains with d-tubocurarine chloride also. Indeed it would be odd if this were not so, since the nerve supply to the abdominal muscles is the same as that of a major portion of the intercostal group. Paralysis of one group should be accompanied by paralysis of all muscles similarly innervated.

The outstanding pharmacologic advantage of the decamethonium compounds is the apparent absence of histamine-like effects. It is our belief that sequelae resulting from the ability of curare drugs to liberate histamine occur more often than is recognized or reported. Admittedly, reactions to H-substance are less intense during general anesthesia. Nevertheless, hypotension, capillary damage and bronchospasm can be expected in a small percentage of cases. In the unanesthetized or lightly anesthetized subject the hazard is increased. Hobson and Prescott (8) reported that 5 of 200 patients given d-tubocurarine chloride prior to electroconvulsion therapy developed bronchospasm. In a series of 40 patients subsequently treated in a similar fashion, one exhibited such a response. Davies and Lewis (6) likewise described a

† Italics ours.
case of bronchospasm following administration of d-tubocurarine. In the hands of these two groups of workers decamethonium salts were without complication when given to the same patients. In addition to the absence of bronchospasm, the lack of a blood pressure lowering action is welcome. The difference in reaction to these two compounds after intra-cutaneous injection reported by Hewer et al. (7) and confirmed by us is striking.

From a purely practical viewpoint the decamethonium compounds are useful for the following reasons: freedom from local irritation, absence of precipitation when used with pentothal solutions and ease of synthesis.

These substances can be expected to be of use to research workers anxious to abolish muscular activity during experimental procedures. Curare and its derivatives have been frequently used for this purpose, the animal being placed on artificial ventilation during the drug action. The apparent localization of activity of decamethonium salts to the nerve-muscle junction should make this drug superior to curare for this purpose. The investigator's results will no longer be suspected because of curare's ganglion blocking action, or its ability to liberate histamine. This will be of particular importance in studies involving blood flow and metabolism.

Both the curare group and the decamethonium salts block conduction across the myoneural junctio. There are, however, important differences as one analyzes this action. The paralytic effect of curare is antagonized by anticholinesterase compounds and is potentiated by ethyl ether. Neither of these attributes is characteristic of decamethonium salts. The implication is that there are fundamental differences between the two types of drugs, further analysis of which may throw light on the basic problems of muscle tone and muscular relaxation.

Summary

Decamethonium bromide has been administered for the production of muscular relaxation of 250 surgical patients. Satisfactory degrees of muscular flaccidity were produced in all but 2 cases. There were no instances of bronchospasm or hypotension following the injection of this drug.

Because of the lack of histamine reactions, its free miscibility with pentothal, the absence of local irritation, and the stability and ease of manufacture of the compound, decamethonium bromide is recommended for further clinical trial in instances requiring administration of a myoneural blocking agent.

REFERENCES


