AN EVALUATION OF SUCCINYLCHOLINE •†‡

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Most therapeutic agents pass through a period of overuse and then the period of overenthusiasm is often followed by a period of reaction and disappointment. A number of years may be required before the true usefulness of a specific drug is finally evaluated.

Curare has followed this pattern rather closely since its introduction into clinical medicine in 1939 (1) and into anesthesiology in 1942 (2). Now, exactly fourteen years and hundreds of papers later, we realize that this valuable drug may, under certain circumstances, cause morbidity and mortality. Its ability to liberate histamine and its ganglionic blocking action have in some patients caused bronchiolar spasm and severe fall in blood pressure (3, 4, 5). The curariform properties of ether are such that injections of curare into patients receiving ether may cause marked hypotension (6). Curare has definite cumulative action and depression of respiratory muscle activity may extend into the postoperative period.

With the introduction of synthetic muscle relaxants, especially syncurine®, it was hoped that the disadvantages of curare would be absent. Syncurine does not liberate histamine (7, 8) and potentiation of its effect by ether does not occur (9). However, irregularity of action of syncurine and the prolonged respiratory depression which may accompany its use (10) have greatly decreased its popularity.

In light of experiences with other muscle relaxants, critical evaluation of newcomers in the group is essential. The effectiveness of the drug, the specificity of its action at the neuromuscular junction, the duration of action, the side effects exhibited, and whether or not the drug makes the conduct of general anesthesia more or less confusing than do other relaxants must be determined. We have attempted to answer these questions regarding succinylcholine chloride.

Description

Succinylcholine chloride consists of two molecules of acetylcholine chloride linked together at the alpha methyl group. It is a de-
polarizing muscle relaxant and its action at the myoneural junction resembles that of acetylcholine and syncurine (11). Although curare and syncurine are excreted largely unchanged by the kidneys (12), it is believed that succinylcholine chloride is hydrolyzed by the plasma cholinesterase to inert choline and succinic acid (13, 14). The brevity of action of succinylcholine chloride is attributed to its mode of destruction.

METHODS

Six hundred and fifty surgical patients received succinylcholine chloride. These patients were entirely unselected and 65 were in poor physical condition because of cardiac, pulmonary, metabolic or other diseases. Six hundred of these patients were studied in detail. Ages ranged from 6 years to 81 years (see table 1). Almost all types of operative procedures were included (table 2).

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>TABLE 2</th>
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<tbody>
<tr>
<td>AGE: RANGE 6-81 YEARS</td>
<td>TYPES OF OPERATIONS</td>
</tr>
<tr>
<td>Site</td>
<td>Number of Cases</td>
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<tr>
<td>Number of Cases</td>
<td></td>
</tr>
<tr>
<td>1. Head and neck</td>
<td>179</td>
</tr>
<tr>
<td>2. Thoracic</td>
<td>82</td>
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<tr>
<td>3. Abdominal</td>
<td></td>
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<tr>
<td>A. Upper</td>
<td>172</td>
</tr>
<tr>
<td>B. Lower</td>
<td>90</td>
</tr>
<tr>
<td>4. Perineal</td>
<td>5</td>
</tr>
<tr>
<td>5. Extremity</td>
<td>25</td>
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<tr>
<td>6. Miscellaneous</td>
<td>47</td>
</tr>
</tbody>
</table>

The majority of the patients received morphine or demerol® plus atropine or scopolamine in suitable doses one hour before induction of anesthesia. General anesthetic agents used included nitrous oxide, ethylene, cyclopropane, ether, sodium pentothal®, and trichloroethylene alone and in a wide variety of combinations. A 10 per cent solution of cocaine hydrochloride was used for topical anesthesia of the pharynx and larynx in 50 patients. An attempt was made to keep each patient in early second plane anesthesia and to produce muscular relaxation with succinylcholine chloride. For some operative procedures in which muscular relaxation was not required, succinylcholine chloride was used to decrease the quantity of general anesthetic used or to insure a quiet operative field.

Respiratory rate, depth and pattern were noted as was the duration of apnea and of intercostal muscle depression when such occurred. The degree of relaxation produced in jaw and abdominal muscles was observed as was the quantity of succinylcholine chloride required to produce such relaxation. An attempt was made to evaluate the effect of the drug on the sensitivity of the larynx.

Circulatory alterations produced by succinylcholine chloride were
studied in the preoperative period before surgical stimulation and changes in blood volume. An intravenous barbiturate followed by succinylcholine chloride was given to 80 patients prior to intubation. The effects of the drugs and of the intubation on blood pressure, pulse rate and electrocardiographic tracings were noted at one minute intervals. Ten adults were given just enough sodium pentothal to put them to sleep. They then received 200 mg. of succinylcholine chloride every two minutes for five injections; that is, 1000 mg. was given in ten minutes. Blood pressure, pulse rate and electrocardiographic tracings were taken every minute.

A group of mice was given doses of curare, syncurine and succinylcholine chloride which caused a degree of muscle paralysis that prevented their hanging to an inverted wire screen. The animals were tested at definite intervals and the period of time during which their muscles were incapable of sustained activity was noted.

Results

Dosage. For endotracheal intubation 20 to 80 mg. of succinylcholine chloride was required when given by single injection. When given by the continuous drip of a 0.1 per cent solution, dosage ranged from 20 mg. to 400 mg., with an average of 78.3 mg. The presence or absence of a supervisor to regulate the rate of drip for the resident or student anesthetist markedly influenced the dosage given. The Harvard microflow regulator was of assistance in adjusting the rate of administration.§

Maintenance doses were given by the continuous drip method. Fifteen to 20 drops per minute was found to be adequate to decrease reaction to an endotracheal tube and to minimize the quantity of general anesthetic required. The number of drops required for intercostal lag and abdominal muscular relaxation varied from 28 to 60 per minute with 28 to 32 appearing to be the requirement in the average patient. For a specific patient the margin between intercostal lag and apnea was narrow; in many instances 28 drops per minute produced respiratory lag while 32 produced apnea.

Total dosage of succinylcholine chloride varied with the patient, the type and duration of the operative procedure, with the general anesthetic agents used, and with the anesthetist. The largest total dose given was 1900 mg. for a four hour resection of the sigmoid; 1800 mg. was given for a nine hour total gastrectomy and splenectomy.

Duration of Action. When given rapidly by single injection, the onset of action of succinylcholine chloride, as evidenced by fasciculatory muscle movements, was in fifteen to thirty seconds. Such fasciculations continued for approximately thirty seconds; their disappearance marked the onset of maximal muscular relaxation which persisted

for three to five minutes. With less rapid injections muscular relaxation developed in one to two minutes, lasted three to five minutes and was then abruptly gone.

Neither cumulative action nor tachyphylaxis was demonstrated in this series. The number of drops per minute of the 0.1 per cent solution required to produce a given effect in a specific patient tended to remain constant for the duration of the operative procedure.

Effect on Respiration. Respiratory rate was unaltered. Respiratory depth decreased as the respiratory muscles became paralyzed; muscle paralysis took place in the same order as seen with curare and syncurine. Respiratory movements were smooth unless partial paralysis of the diaphragm was produced; this was in contrast to the jerky respirations frequently seen with syncurine.

When sufficient drug was given for abdominal relaxation, assistance of respiration was necessary. A second individual could easily adjust the continuous drip in such a way that muscle relaxation but not apnea was present; this was mechanically difficult for the individual administering the general anesthetic and apnea occurred at some time during most upper abdominal procedures. Apnea was especially prone to occur when cyclopropane was the general anesthetic agent administered. Patients who were carried on “controlled respirations” required from two to forty-eight minutes for resumption of spontaneous respirations when such were desired. The average

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**TABLE 3**

<table>
<thead>
<tr>
<th>Blood Pressure and Pulse Change from Control Values Following Thiobarbiturate, Succinylcholine Chloride and Endotracheal Intubation</th>
<th>0 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Changes</strong></td>
<td>Thiobarbiturate</td>
</tr>
<tr>
<td>Systolic BP. (Suntil)</td>
<td>▲</td>
</tr>
<tr>
<td>Diastolic BP.</td>
<td>●</td>
</tr>
<tr>
<td>Pulse</td>
<td>△</td>
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</tbody>
</table>

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duration of apnea was seven minutes; it persisted for more than ten minutes in twenty patients. In one patient diaphragmatic activity returned in eighteen minutes but an additional twelve minutes was required for resumption of intercostal activity.

**Effect on Circulation** (table 3). In the 80 patients studied preoperatively, rapid injections of surital® or pentothal sodium, in mean doses of 312 mg. and 328 mg. respectively, caused a marked decrease in blood pressure. This practice of rapid injection of barbiturates has been modified in our clinic. When succinylcholine chloride in doses of 20 to 100 mg. was injected three to five minutes following the barbiturate and after the pressure had more or less stabilized, systolic and diastolic pressures rose and the pulse pressure narrowed. As can be seen in table 3, blood pressure levels were still below control values. Very little change occurred in pulse rate. Two of the 80 patients had ventricular premature contractions attributable to succinylcholine chloride and two developed a transient nodal rhythm.

The injection of 1000 mg. of drug over a ten minute period (table 4) was followed by moderate rises in systolic and diastolic pressures with some slowing of the pulse. One patient had occasional premature ventricular extrasystoles. No other alterations of cardiac rhythm took place.

**Muscular Relaxation.** Abdominal relaxation was considered good to excellent in all cases. In 6 instances the jaw was poorly relaxed; neither anoxia nor hypercarbia was present in these patients.

**Effect on Sensitivity of Larynx.** Succinylcholine chloride appeared to cause no decrease in the activity of the laryngeal reflex at the time of intubation. During maintenance, however, minimal doses of 15 to 20 drops per minute of the drug markedly decreased the patient’s reaction to the tube. Laryngospasm developed in one patient when the succinylcholine chloride drip was stopped momentarily so that blood could be pumped. The injection of enough succinylcholine

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Control Values</th>
<th>After NA Pentothal</th>
<th>After Succinyl</th>
<th>Duration of Apnea in Min</th>
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<tbody>
<tr>
<td>1</td>
<td>140/80</td>
<td>110/80</td>
<td>155/106</td>
<td>60</td>
</tr>
<tr>
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<td>120/80</td>
<td>110/86</td>
<td>120/88</td>
<td>48</td>
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</tbody>
</table>
chloride to cause apnea relaxed the patient’s vocal cords. The plane of general anesthesia did not vary during this episode. Spraying of the vocal cords with 10 per cent cocaine hydrochloride abolished or markedly decreased bucking on the endotracheal tube at the time of intubation.

Miscellaneous Effects. No evidence of histamine liberation was seen. Hiccups developed in 6 patients during upper abdominal procedures; they subsided in 5 cases when enough succinylcholine chloride to produce apnea was given. In the sixth case hiccups continued in spite of apnea; discontinuing the succinylcholine chloride drip and deepening anesthesia with ether proved curative. Excessive salivation was seen four times; three times following intubation and once in the absence of any laryngeal instrumentation. Secretions persisted throughout the procedure in each instance but were not particularly troublesome. Muscle fasciculations were seen only when the drug was injected rapidly.

There were no deaths attributable to succinylcholine chloride in this series.

Our studies on mice are not complete. Data obtained thus far indicate that mice given paralytic doses of curare do not regain full muscle power for three to fourteen hours. Following administration of syncurine such return takes place in fifteen to thirty minutes and in two to four minutes after succinylcholine chloride is given.

Discussion

Succinylcholine chloride is an effective drug; it produces muscular relaxation quickly and consistently. Preliminary studies in mice indicate that its effect on muscle activity is over in two to four minutes. In human beings this brevity of action was seen in 96.7 per cent of patients. In 3.3 per cent apnea persisted from ten to forty-eighty minutes. It is possible that hyperventilation and acapnia were responsible for persistence of apnea in some cases, while in others it was attributable to drug action. Whether prolongation of effect of the drug was the result of peripheral or central effect cannot be stated. Ellis et al. (15) found that depression of the respiratory center by succinylcholine chloride may occur. Several cases of prolonged respiratory depression after the use of succinylcholine chloride have been reported by others (16, 17, 18, 19).

The apparent absence of deleterious effect of succinylcholine chloride on the cardiovascular system may well be its outstanding virtue. Consistent elevations of blood pressure were seen following therapeutic doses but were not marked. Elevations following ten to twenty times the usual therapeutic doses were more marked but were not excessive. Sharp rises in pressure such as those reported by Adderley and Hamilton (20) were not seen in this series. Effects on cardiac rhythm were minimal.
AN EVALUATION OF SUCCINYLCHOLINE

Dardel and Thesloff (21), in animal experiments, have shown that "provided respiration is adequately maintained by artificial means, it is possible to administer several thousand times the paralyzing doses of succinylcholine chloride without any demonstrable changes being observed." In our series ten to twenty times the therapeutic dose has produced apnea, a slight rise of systolic and of diastolic blood pressure, and some slowing of the pulse rate. The toxicity of the drug appears to be low.

Side effects such as hiccups and excessive salivation were rare and of little consequence. Muscle fasciculations accompanied only rapid injections of the drug.

We did not observe the sparing effect on respiration reported by Foldes (22). Abdominal relaxation was accompanied by decrease in intercostal muscle activity and respirations usually required assistance. Respiratory depth depended to some extent on the general anesthetic agent used but was always decreased in the presence of intercostal lag or paralysis.

The narrow margin between the amount of drug required to produce the desired amount of muscle relaxation and that which produced apnea requires a careful and precise adjustment of the rate of administration with frequent checks on the rate of flow. The difference between breathing and apnea is frequently a matter of 0.1 ml. per minute. These mechanical maneuvers increase the demands made on the individual administering the general anesthetic. The well-trained anesthetist can accept this additional demand and can achieve excellent results from the standpoint of the patient and the surgeon. For less experienced workers the high incidence of apnea necessitating controlled respirations may make the proper administration of the general anesthetic agent much more difficult. Holaday (23) in 1949 pointed out that the dangers associated with the use of curare are overcurarization and underanesthetization and that more complications are associated with underanesthetization than with overcurarization. This may well be true with succinylcholine chloride. In 3 instances in our series, when apneic patients resumed spontaneous respirations they were found to be too lightly anesthetized, and bronchiolar spasm developed. How frequently and of what consequence reflex responses to stimulation will be in lightly anesthetized patients who are given this nonganglionic blocking muscle relaxant are questions still to be answered.

SUMMARY

Succinylcholine chloride is an effective, nontoxic muscle relaxant which has minimal side effects and does not adversely affect the cardiovascular system.

Very brief duration of action is the rule; prolongation of effect is the exceptional occurrence. Interest focuses on prolonged depres-
sions of respiration and it is highly desirable to know what the over-all incidence will be.

For procedures for which brief periods of relaxation are required, such as intubation, electroshock treatment and abdominal closure, succinylcholine chloride appears to have no peer. For longer procedures this drug is a boon to the experienced anesthetist. However, the very fine adjustment of effect necessary may be a source of confusion for the less adept colleague. Since the majority of anesthetic agents in this country are administered by individuals who are still being trained or who have had limited training in anesthesia, how suitable this drug will be for general use remains to be seen.

ACKNOWLEDGMENT

We wish to thank Dr. Donald S. Scarcles of Burroughs Wellcome & Co. for supplying the succinylcholine chloride used in this study.

REFERENCES

12. Marsh, D. F.: Distribution, Metabolism, and Excretion of D-tubocurarine Chloride and Related Compounds in Man and Other Animals. (To be published.)

PROGRAM

The next regular meeting of the New England Society of Anesthesiologists will be held on Friday, April 9, 1954, at the Hotel Beaconsfield, Boston, Massachusetts.

MORNING SESSION

8:00–12:00 Operative schedules at various Boston hospitals.

AFTERNOON SESSION—Hotel Beaconsfield

2:00–3:00 p.m. Morbidity and Mortality Case Reports—Jacob Fine, M.D., Beverly Hospital, Beverley, Mass.

3:00–4:00 p.m. Effects of Pentothal and Cyclopropane on Cardiac Output and Related Hemodynamics—Benjamin Etsten, M.D., New England Center Hospital, Boston, Mass.

4:00–5:00 p.m. Effects of Ether on Cardiac Output and Related Hemodynamics—William Brewster, M.D., Massachusetts General Hospital, Boston, Mass. Moderator: Morris J. Nicholson, Labey Clinic, Boston, Mass.

EVENING SESSION—Hotel Beaconsfield

7:00–7:30 Business Meeting.

7:30–9:00 The Clinical Use of the Muscle Relaxing Agents in Anesthesia—Francis Foldes, M.D., Mercy Hospital, Pittsburgh, Pennsylvania.