

SYNCURINE (DECAMETHONIUM-BROMIDE): ITS USE WITH PENTOTHAL-SODIUM AND NITROUS OXIDE- OXYGEN ANESTHESIA IN ABDOMINAL SURGERY * †

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SINCE the introduction of curare in anesthesiology by Griffith (1), the search has been on for other muscle relaxants. The object was to find other drugs that are more easily obtainable, are equally good or better muscle relaxants than the curare derivatives and possess less undesirable side effects. In succession, erythroidine (2), myanesin (3) and flaxedyl (4) have been investigated but the results obtained did not prove any of them superior to the curare derivatives.

Starting with the assumption that the paralyzing effect of *d*-tubocurarine chloride (DTC) is due to the presence of two quaternary nitrogen atoms at an optimal distance apart, Barlow and Ing (5) and Paton and Zaimis (6), working independently, prepared a number of bisquaternary ammonium salts in which the two nitrogen atoms were separated by polymethylene chains of different lengths. In the bis-trimethyl ammonium chloride series the paralyzing effect was maximal when the length of the methylene chain was 10. The bromide salt of this compound, decamethonium-bromide, is available for clinical use in a 1 to 1000 solution, under the trade name of syncurine.

Animal experiments with syncurine carried out by Paton and Zaimis (7), and by Castillo and de Beer (8) revealed important differences between the pharmacologic actions of syncurine and DTC. Syncurine showed a much greater potency variation than DTC (table 1) in the different species investigated (7, 8).

In unanesthetized man, Organe, Paton and Zaimis (9) and Grob, Holaday and Harvey (10) found that the intravenous injection of 3.0 mg. of syncurine in sixty to ninety seconds produced the same degree of paralysis that could be obtained by the intravenous injection of 15 to 20 mg. of DTC.

Clinical trials with syncurine in anesthetized patients were carried out by Organe (11), Hewer, Lucas, Prescott, and Rowbotham (12),

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Holaday, Harvey and Grob (13) and Harris and Dripps (14). All observers agreed that syncurine is equally effective when used with the various general anesthetic agents (ether, cyclopropane, pentothal sodium, ethylene and so forth). Following its administration maximal relaxation developed in four to eight minutes. Satisfactory relaxation was present for from ten to twenty-five minutes. No major cardiovascular changes, attributable to syncurine were seen during or after anesthesia. Occasional fluctuation of blood pressure and pulse rate was thought to be the consequence of carbon dioxide accumulation caused by inadequate respiratory exchange (13). Organe was of the opinion that bleeding from cut surfaces was less than after the use of DTC (11). No evidence was found of histamine release from the tissues after intracutaneous injection (12, 14) or intravenous administration (14). Organe (11) believed that laryngeal irritability is reduced by syncurine, and Hewer et al. (12) assumed that it might have some vagal inhibitory effect. The reports on postoperative complications were favorable. There were no operative or postoperative deaths caused by syncurine in the combined series of 657 cases so far reported. The incidence of major pulmonary complications was not increased and seemed to be less than after DTC (11). Similarly, nausea and vomiting, ileus, abdominal distention and urinary retention were not more frequent following its use.

TABLE 1

THE RELATIVE POTENCY OF C-10 COMPARED TO DTC BASED ON THE EXPERIMENTS OF PATON AND ZAIMIS (7) AND CASTILLO AND DE BEER (8)

Animal	Potency of C-10 Compared to DTC
Mouse	0.25
Monkey	0.33
Rabbit	1.0-1.5
Dog	2.0
Cat	5.0-7.0

Considerable differences of opinion exist, however, between various workers with regard to dosage, the relationship of muscular relaxation and respiratory depression. The initial dose recommended was 1 to 2 mg. by Holaday et al. (13), 3 mg. by Organe (11), 2 to 4 mg. by Harris and Dripps (14) and 3 to 5 mg. by Hewer et al. (12). Subsequent doses recommended by the various workers ranged from 0.5 to 3.0 mg. at ten to twenty-five minute intervals. With the exception of 4 cases reported by Harris and Dripps (14), no cumulative effects of syncurine have been observed. Hewer et al. (12) claimed that muscular relaxation comparable to that produced by DTC can be obtained only by doses that will produce respiratory paralysis. In contrast to this Holaday et al. (13) reported satisfactory relaxation in 130 of 158 abdominal operations without a single instance of apnea. The experiences of Organe (11) and Harris and Dripps (14) seem to be between these two extremes. They found that in most instances good abdominal

relaxation could be achieved without apnea, but in some cases satisfactory operating conditions were obtainable only with doses of syncurine that produced respiratory paralysis. All workers agree that good muscular relaxation was almost always accompanied by some degree of reduction in the tidal volume of respiration. An increase of the respiratory rate was observed by Harris and Dripps (14) after small doses of syncurine, and by Hewer et al. (12) on recovery from respiratory paralysis. There is also a wide variety of opinions regarding the efficacy and safety of pentamethonium-iodide (C-5) as an antidote. Organe (9, 11) believed that C-5 is effective but its use is unnecessary in clinical anesthesia. Hewer et al. (12) used C-5 in 30 to 50 mg. doses on 8 patients. In 6 of these cases the return of the respiration to normal was not markedly accelerated, and in 3 patients severe circulatory collapse developed.

TABLE 2
TYPES OF OPERATIONS

	Number of Cases
Subtotal gastrectomy	17
Cholecystectomy, exploration of common bile duct	84
Other upper abdominal operations	26
Colostomy, colectomy, combined abdominoperineal resection	15
Appendectomy	36
Hysterectomy	22
Various gynecologic operations	4
Total	204

The mode of action of syncurine has not been clarified as yet. It probably acts also at the neuromuscular junction but, unlike DTC, not through interference with the acetylcholine transmission system, since its effect is not counteracted by eserine and neostigmine (7). That the mode of action of syncurine is different from that of DTC is emphasized by the observation of Paton and Zaimis (6) who found that its potency was halved when it was used immediately after two-thirds of the paralyzing dose of DTC.

MATERIAL AND METHODS

Our observations were based on experiences with 204 patients who were anesthetized with pentothal-sodium-nitrous oxide-oxygen-syncurine for intraabdominal operations (table 2). No selection was made with regard to the physical condition of the patients, and this form of anesthesia was used whenever general anesthesia was indicated. The age of the patients ranged from 14 to 85 years with an average of 48.4 years (table 3). There were 63 males and 141 females in this series.

Patients were premedicated with a short acting barbiturate ninety minutes, and with a combination of an analgesic and a parasympathico-

lytic agent forty-five to sixty minutes preoperatively. When the patient did not appear to be optimally sedated on arrival to the operating room an additional small dose of the analgesic agent was administered intravenously.

Anesthesia was induced with a 2.5 per cent solution of pentothal-sodium. The amount necessary to produce stage III, plane I anesthesia was noted. As soon as the patients were asleep 1.0 to 3.0 cc. (1.0 to 3.0 mg.) of syncurine was given intravenously and administration of oxygen in a closed circuit was started to keep the patients well oxygenated and to observe any change in the respiratory rate and depth. Two to three minutes after the syncurine administration, one-third to one-half of the initial pentothal dose was injected and the larynx was sprayed under direct vision with a small quantity of 2 per cent pontocaine solution. If the cords were open pontocaine was sprayed down the trachea. Following this, an oral airway was inserted and administration of oxygen continued for two more minutes

TABLE 3
AGE DISTRIBUTION OF PATIENTS

Age Group years	Number
11-20	10
21-30	24
31-40	32
41-50	47
51-60	44
61-70	36
71-80	10
81-90	1
Total	204

to allow the pontocaine to exert its surface action. When necessary an additional dose of pentothal was administered and shortly thereafter an endotracheal tube inserted. At that time, if it had not been possible to spray into the trachea because of adducted cords, the trachea was sprayed before the insertion of the tube. After intubation oxygen was administered for twenty to thirty seconds. The bag was washed out three times with a 3 to 1 nitrous oxide-oxygen mixture and then a mixture of 60 per cent nitrous oxide and 40 per cent oxygen (500 cc. of nitrous oxide and 600 cc. of oxygen, assuming that the metabolic requirement for oxygen was 300 cc.) was administered in a closed circuit. With this method of induction, 79 per cent of the patients maintained spontaneous but somewhat depressed respiration. Assisted respiration was used throughout. Relaxation was maintained by repeated injections of fractional doses, 0.5 to 1.0 mg., of syncurine at ten to thirty minute intervals. Occasionally a larger dose was necessary to facilitate the closure of the peritoneum. Pentothal sodium was given ac-

cording to need; voluntary breath holding and wrinkling of the forehead are good indication for additional pentothal administration.

Usually no more pentothal or syncurine was necessary after peritoneal closure and fair proportion of patients reacted shortly after administration of nitrous oxide-oxygen was discontinued. Before the removal of the endotracheal tube tracheobronchial aspiration was performed. If intercostal respirations were absent at the time of extubation, the patient was kept in the operating room and oxygen was administered until normal respiration was reestablished.

RESULTS

The duration of anesthesia in this series ranged from twenty-five to 480 minutes, with an average of ninety-five minutes (table 4). The amount of syncurine used before intubation was 1.0 to 4.0 mg. In the earlier cases the smallest dose of syncurine used before intubation was 3.0 mg., but this dose produced apnea lasting several minutes in a considerable number of patients. Subsequently, with the exception of

TABLE 4
THE INITIAL AND TOTAL DOSES OF C-10 AND PENTOTHAL SODIUM

	Range	Average
Duration of anesthesia	25-480 minutes	95 minutes
Initial Dose of C-10, mg.	1.0-4.0	2.4
Total dose of C-10, mg.	1.0-22.0	7.0
Dose of C-10 per minute, mg.	0.023-0.361	0.089
Initial dose of pentothal, mg.	200-850	493.0
Total dose of pentothal, mg.	250-2000	1040.0
Dose of pentothal per minute, mg.	2.72-28.8	13.4

very robust patients, the initial dose of syncurine was reduced to 2.0 mg. Additional doses of 0.5 to 1.0 mg. were given at ten to twenty minute intervals as required. Occasionally, when the operative conditions did not require relaxation for longer periods, no additional syncurine was given for as long as sixty minutes. In these cases the initial dose was repeated when relaxation had to be reestablished. The total dose of syncurine ranged between 1.0 and 22.0 mg., averaging 7.0 mg.

With this dosage satisfactory relaxation was obtained in all cases, however not without the development of apnea in 43 (21 per cent) of the patients. In most cases, the apnea developed immediately after intubation and lasted from three to twenty-two minutes (averaging 9.5 minutes). In one patient, to be discussed later, apnea of forty minutes' duration was observed. Once active respiration was reestablished, satisfactory relaxation could be maintained with fractional doses of syncurine without further apnea. With optimal relaxation, the respiratory depth was usually decreased owing to intercostal paralysis and assisted respiration was used in the majority of patients. This

was especially true for upper abdominal operations. In lower abdominal procedures, satisfactory relaxation could be obtained almost always without perceptible embarrassment of the respiratory depth. Respiratory exchange was judged to be normal in 76 per cent and moderately depressed in 24 per cent of the cases at the end of operation.

Perhaps the most gratifying experience with syncurine was the lack of undesirable circulatory effects incidental to its use when adequate respiratory exchange was maintained. For practical purposes the blood pressure and pulse rate remained unchanged in most of the patients. No alarming hypotension or hypertension was seen in any of our cases.

There was no incidence of bronchospasm in this series. Syncurine was used purposely in a 61-year-old asthmatic man for subtotal gastrectomy, without any ill effects. On the other hand laryngeal irritability did not seem to be decreased after administration of syncurine.

The plane of pentothal anesthesia could be kept light enough that the patients, with a few exceptions, awakened within a reasonably short time after the end of the operation. Thirty-five patients were conscious when administration of nitrous oxide-oxygen was discontinued and the remaining 169 recovered in five to 184 minutes (average thirty-nine minutes).

TABLE 5
POSTOPERATIVE COMPLICATIONS

	Number	Per cent
Atelectasis	11	5.4
Excessive bronchial secretions	38	18.6
Nausea and vomiting	34	16.7
Abdominal distention	39	19.1
Urinary retention	49	24.0

With four exceptions, there were no indications of cumulative effect or prolonged action of syncurine. One patient, a 68-year-old emaciated man scheduled for subtotal gastrectomy, was erroneously too heavily premedicated (nembutal $1\frac{1}{2}$ grains, morphine sulfate $1/6$ grain, scopolamine $1/150$ grain). Because the patient was too depressed to cooperate, the level of the spinal anesthesia was inadequate and had to be supplemented with pentothal sodium-nitrous oxide-oxygen-syncurine. A dosage of 2.0 mg. of syncurine and 200 mg. of pentothal sodium was administered and intubation performed. Satisfactory relaxation was obtained for forty minutes. During that time an additional 100 mg. of pentothal sodium was given and vagotomy performed because the ulcer had healed since the previous roentgenologic examination. Forty minutes after the original dose an additional 1.0 mg. of syncurine was administered to facilitate closure. Soon after this, apnea developed that lasted forty minutes. The patient did not regain consciousness for 180 minutes. Otherwise the postoperative course and convalescence were uneventful.

The postoperative complications are listed in table 5. The incidence of postoperative atelectasis (5.4 per cent) was not greater than in comparable groups of patients operated upon under other forms of anesthesia. All 11 instances of atelectasis were observed in patients who underwent subtotal gastrectomy or cholecystectomy. The relatively high incidence of atelectasis can be explained by the prevalence of chronic respiratory diseases in our geographic area. No major circulatory complications were seen in the postoperative period.

There were two deaths in this series. Both patients arrived in the operating room in coma and moribund. The first, a 72-year-old man, had massive peritonitis as a result of accidental perforation of the sigmoid in the course of sigmoidoscopy. The second patient, a 69-year-old man, had intestinal obstruction of several days' duration. At operation a large perforating carcinoma of the sigmoid was found with peritonitis and extensive liver metastases. Colostomy was performed on both patients, but both died a few hours after operation without regaining consciousness.

DISCUSSION

Syncurine has been used to obtain muscular relaxation during anesthesia by several workers (11, 12, 13, 14) using a variety of agents. Most of these anesthetic agents themselves produce muscular relaxation. Furthermore, syncurine was also employed in connection with operative procedures in which muscular relaxation was not required (12). In order to evaluate the muscle relaxing properties of syncurine, we restricted its use to intra-abdominal surgical procedures requiring good muscular relaxation, and only used it with nitrous oxide-oxygen and pentothal sodium, which in the concentration and dosage employed produce little or no muscular relaxation.

Although it has been shown by Paton and Zaimis (7) that paralytic doses of syncurine do not produce autonomic block, Hewer et al. (12) assumed that syncurine has a slight inhibitory effect on the vagus. Harris and Dripps (14) reported that the vocal cords seemed to be less irritable when syncurine was used than following administration of DTC. Our impression seemed to be the contrary. We found that when local anesthetization of the cords and the trachea was inadequate there was a high incidence of voluntary breath holding that could be confused with apnea caused by syncurine, and which could be abolished by increasing the depth of pentothal anesthesia. We believe that local anesthetization of the pharynx, larynx and trachea is necessary for the smooth conduct of pentothal sodium-nitrous oxide-oxygen-syncurine anesthesia.

Hewer et al. (12) reported that muscular relaxation, comparable to that produced by DTC, could be obtained only with doses of syncurine that paralyzed respiration. Harris and Dripps (14) found that in many upper abdominal operations respiratory paralysis and controlled respiration were necessary for profound muscular relaxation.

Our experience in this respect seems to be closer to that of Organe's (11) who found that it is seldom necessary to paralyze respiration to obtain adequate muscular relaxation for peritoneal closure. Except for brief periods of apnea which occurred immediately after intubation in some of our cases, adequate muscular relaxation could almost always be obtained without respiratory paralysis.

Our clinical impressions seem to corroborate the lack of the histamine liberating properties of syncurine reported by others (11, 12, 13, 14). We used syncurine-pentothal sodium-nitrous oxide-oxygen anesthesia for subtotal gastrectomy on a 61-year-old asthmatic patient who was also a chronic alcoholic. Although the preoperative wheezing was not abolished, the respiratory exchange and oxygenation of the patient were satisfactory throughout the five-hour operation.

The use of pentothal sodium-DTC solutions containing fixed proportions of both drugs has been advocated by Baird (15), Knight (16) and Baird et al. (17). Organe (11) mentioned the use of a 250 to 1 solution of pentothal sodium-syncurine. On the basis of pharmacologic considerations and clinical experience we do not believe that the use of pentothal sodium solutions containing either DTC or syncurine in fixed proportions is justified. Whatever the agent or method employed it should be the goal of the anesthesiologist that the anesthetic administered should be readily controllable. It needs no emphasis that there is a considerable variation in the requirements for pentothal sodium of various patients according to age, constitution and habits (use of alcohol, sedatives, analgesics and so forth). Variation also exists in the DTC and syncurine needs of various patients, but no proof is available that sensitivity to pentothal sodium and to muscle relaxants varies in the same direction. Furthermore, in the course of an operation it is often necessary to increase muscular relaxation or the depth of general anesthesia alone. With the use of fixed mixtures this is not possible. Another factor that enters into the problem is that pentothal sodium has a definite cumulative effect and in longer operative procedures proportionately less and less pentothal sodium has to be used per unit of time. Although DTC also seems to have some cumulative effect, present evidence indicates that this is not the case with syncurine. The observant anesthetist can readily determine whether the patient needs more pentothal sodium, more syncurine, or both, and can administer it as necessary, thereby avoiding overdosage with one or the other of the two agents. To demonstrate the wide variation of the needs for pentothal sodium and syncurine of different patients, the ratio of the amount of pentothal sodium to the amount of syncurine used before intubation and the ratio of the two drugs used during the whole operative procedure were calculated. The figures in table 6 bring out two facts. First that there is a wide variation in the ratio of pentothal sodium to syncurine both before intubation and during the whole operative procedure, and second that relatively less pentothal

sodium and more syncurine have to be used in the course of the whole operation than early in anesthesia.

On the basis of the limited number of cases here presented, we believe that syncurine has a useful place in anesthesiology. More experimental work is necessary to clarify the mechanism of action of syncurine which seems to be fundamentally different from that of DTC, and more clinical observations will have to be made to arrive at the best possible methods of administering this drug. At present it seems safe to say that syncurine used with nitrous oxide-oxygen and pentothal sodium anesthesia possesses the following advantages: (1) It is short acting and therefore controllable. The danger of prolonged postoperative respiratory depression seems to be reduced. (2) In therapeutic doses it does not liberate histamine and does not block the autonomic ganglions. It does not produce major circulatory changes and so far no instance of bronchial spasm has been reported with its use. (3) It can be heat-sterilized; it does not deteriorate on standing, and it is readily miscible with the common intravenously injected drugs used in anesthesiology.

TABLE 6

RELATIONSHIP BETWEEN PENTOTHAL SODIUM AND C-10 REQUIREMENT

	Range	Average
Ratio of the amount of pentothal sodium to the amount of C-10 used before intubation	100.0-300.0	224.0
Ratio of the amount of pentothal sodium to the amount of C-10 used during anesthesia	81.0-300.0	160.0

The chief disadvantage of syncurine is that occasionally its muscle relaxing effect wears off abruptly. This at times can be troublesome to the surgeon. Careful observation of the respiratory depth, however, usually gives sufficient warning to anticipate and prevent this complication. A further drawback to the use of syncurine is the hitherto unexplained prolonged respiratory depression reported by Harris and Dripps (14) and also seen by us on four occasions.

SUMMARY

Syncurine has been used to obtain muscular relaxation for intra-abdominal operations in 204 patients anesthetized with a combination of pentothal sodium and nitrous oxide-oxygen.

Good muscular relaxation was obtained in all cases. No unwanted side effects (hypotension, bronchospasm, and so forth) were observed and syncurine was well tolerated by poor risk patients undergoing major surgical operations.

The incidence of postoperative circulatory complications seemed to be less, and respiratory complications were not more frequent than in

comparable groups of patients anesthetized by other agents and methods.

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