THE USE OF CURARE IN ANESTHESIA; A REVIEW OF 100 CASES *

Frank Cole, M.D.

Minneapolis, Minn.

The term "anesthesia" was originally used to mean relief from pain, but modern technical usage of the word implies muscular relaxation that facilitates many difficult abdominal surgical procedures. This effect is usually produced by deepening the anesthesia, bringing about a higher concentration of the anesthetic agent in the blood. It has more recently been obtained by the use of "combined anesthesia," or "balanced anesthesia," wherein the patient is put to sleep after the required relaxation has been accomplished by regional nerve block, usually spinal anesthesia. In this series of 100 cases, the relaxation of abdominal muscles was obtained by the use of curare, following the anesthetization of the patient with a general anesthetic agent, cyclopropane being used in all but two cases. Curare was often used after a spinal nerve block had been done and the patient anesthetized, but when sufficient time had elapsed to permit the lessening or actual disappearance of the spinal effect, evidenced by the return of abdominal muscle tension.

To obtain relaxation and anesthesia by the use of one drug requires a higher concentration of the agent in the blood, and, in the case of an inhalant, in the inspired atmosphere; it imposes on the patient the penalties of an anesthesia deeper than is necessary to obtain merely anesthesia. When the relaxation is provided by another means, whether it be the production of regional analgesia or the use of curare, a lighter anesthesia may be maintained, which should, theoretically, improve the patient's operative and postoperative course.

Curare is obtained by brewing the various parts of several species of the Strychnos genus. Commercially, it has hitherto been available as a dark brown, shiny, resinous substance. Intocostrin, the Squibb extract used in this series, is a clear, transparent, amber liquid, packaged in 5 cc. rubber-stoppered ampules, containing a 2 per cent sterile solution of a standard drug. The activity of intocostrin is due almost entirely to the presence of a crystallizable substance, d-tubocurarine chloride, a solution of which is now available for use in investigations (1).

In the early history of curare it was used by South American Indians in hunting and possibly in fighting, and in the physiological lab-

* From the Division of Anesthesiology, University of Minnesota Hospitals, Minneapolis, Minnesota.

oratory. Hoffmann (2) administered curare, unsuccessfully, in the treatment of tetanus, in 1879; he was able to control the seizures, but not without severe respiratory depression, for which he performed tracheotomy and artificial respiration. Hoche (3) used it to treat tetany, in 1894; and it was used by L. B. Cole in 1934, by Mitchell in 1935, and by West in 1936, in the treatment of tetanus. Burman administered curare in 1939, in treating spastic states. It was first used in its present form by Bennett, in 1940, for the prevention of serious injuries often encountered in convulsive shock therapy in psychiatry (4). Griffith and Johnson, in 1942, reported its first use in anesthesia; it was their practice to give single doses in cases of difficult abdominal closure (5). Cullen, in 1943, was the first to report a series of cases dealing with the use to which it has since been put at this hospital (6). The newness of the use of this drug in man is exemplified by such statements in the 1942 printing of Goodman's and Gilman's "The Pharmacological Basis of Therapeutics" (7) as, "Curare is an important pharmacological tool for laboratory investigations, but as yet it has no well-established therapeutic uses"; and "Curare and its alkaloids have no valid, well-established clinical uses."

The curare effect is the interruption of nerve impulses at the myoneural junction, so that the muscle will respond neither to injected acetylcholine nor to stimulation of its nerve. The action is entirely peripheral, so that a nerve bathed in curare will still conduct impulses. The curare effect, neutralization of the acetylcholine reaction, the fundamental neuromuscular stimulation mechanism, has been shown to be inhibited by prostigmine; prostigmine is known to inhibit cholinesterase, which, in turn, destroys acetylcholine, and thus to restore the acetylcholine preponderance at the myoneural junction.

Muscles are affected in the following order: first, those supplied by cranial nerves, followed by those of the trunk and extremities, and finally those of respiration; the diaphragm is the last muscle to be paralyzed. Subjectively, the effects of curare on an unanesthetized, unpremedicated patient are, in the order of appearance, weakness of the eyelids, strabismus with diplopia, weakness of throat and jaw muscles with inability to swallow or to cough, inability of the patient to raise himself, weakness of arms and legs, and finally respiratory paralysis. Recovery occurs, as in a too high spinal block, in the reverse order, so that the diaphragm and the intercostal muscles are the first to regain their function. Under anesthesia, the only effect seen with a proper dose is the immediate relaxation of the abdominal muscles; with a larger dose, respiratory depression. The incidence of laryngospasm is believed to be smaller when curare has been given; endotracheal intubation may be facilitated by its use, and curare may be used in the treatment of laryngospasm.

Substituting curare for the spinal block usually employed in conjunction with cyclopropane anesthesia is of some advantage in avoiding

the fall of blood pressure commonly seen in spinal analgesia. No significant blood pressure changes were found in the entire series. The use of curare eliminates, also, the headache, nausea and vomiting, and many other untoward signs and symptoms complicating subarachnoid nerve root block, as well as the possibility of permanent damage to the spinal cord or spinal nerves themselves, rare but dangerous complications. It renders unnecessary the psychic trauma attending the performing of this block on a conscious, often apprehensive, patient.

Curare cannot be used as a substitute for spinal analgesia, as it is less effective in producing relaxation when used without anesthesia or preanesthetic medication; and it is in no way an anesthetic drug, but simply a muscle paralyzer.

Two absolute contraindications for the use of curare are myasthenia gravis and the inability of the anesthetist to perform artificial respiration. The anesthetist must be definitely convinced, before administering curare, of his ability to care for the respiratory depression that may ensue by performing artificial respiration, and must be so convinced only, before injecting this drug, by actually inflating the anesthetized patient's lungs. While the physiologic antidote for a toxic dose of curare is physostigmine or prostigmine, 1 cc. of a 1:2000 solution of the latter being injected intravenously, neither of these drugs was used in the entire series, artificial respiration being easily performed and proving quite satisfactory. Controlled breathing is a necessary part of the anesthetist's armamentarium. Artificial respiration is best carried out in these cases, as in any operating-room situation where it is demanded, by intermittent manual compression of the breathing bag on a gas machine, using either a tight fitting face mask or an endotracheal tube.

Curare is partly destroyed by the liver and in part eliminated unaltered by the kidney. A relative contraindication for the use of this drug is the presence of impaired renal function, which might serve to heighten the effect of an otherwise harmless dose (7).

The patient's age, vigor, weight, and depth and rate of respirations were considered in calculating the dose. Based on weight alone, doses of 1 mg. per kilogram and of ½ to ⅔ mg. per pound of body weight have been used. In this connection, it may be mentioned that larger initial doses were used in the first half of the cases in this series than in the second, many 100 mg. doses being given at the start of the series; at present, doses of 60 to 70 mg. are commonly given at the beginning of an operation. Doses of 40 to 60 mg. were used to maintain relaxation when the effect of the first injection had disappeared.

All injections were intravenous and were made rapidly, no single administration requiring more than ten seconds. The initial injection in each case was not made until relaxation was of some advantage, for the following reasons. First, the effect of the curare was almost in-

variably present within one minute following its intravenous administration. Second, the duration of its effect was known to be limited. Third, the tension of the abdominal muscles and tightness of the peritoneum could be seen, and the onset and degree of relaxation observed. The drug was therefore given as the peritoneum was about to be opened, or at the time of its opening. In those cases in which a spinal block had been done, curare was administered as soon as the wearing off of the spinal effect became apparent. It was interesting to note the long duration of relaxation obtained by the nupercaine-dextrose spinal block used here in gastric resections, the average being three and three-fourths hours. Curare is also effective when injected intramuscularly, but this method of administration entails a fifteen-minute wait for relaxation. No effect is obtained when it is taken by mouth in the presence of an intact mucous membrane.

Undesirable side effects consisted entirely of respiratory depression. No noteworthy circulatory disturbances were encountered in the entire series. The respiratory depression was manifested by a diminution of depth of respiration and (as intercostal function decreased) a jerkiness, which produced a picture typical of an overdose of ether. In some cases, the depression was severe, so that very little movement of the breathing bag could be seen, and in a few cases, total apnea resulted. In the presence of apnea, or when respiratory excursion was too shallow to carry on oxygenation efficiently, artificial respiration was employed until normal respiratory function had returned to a sufficient degree; the average period of severe respiratory depression was ten minutes.

Sodium pentothal was the anesthetic agent in two cases. Severe respiratory depression was seen in one of these cases; unaltered breathing in the other. Ethyl ether, pentothal, and tribromethanol have been shown to possess curariform properties, in the sense that they inhibit the contractile response of a muscle in a dog to an injection of acetylcholine and to an electric stimulation of the controlling nerve (8). Of these three anesthetics, ether is the worst offender; high blood concentrations of pentothal and avertin are required to demonstrate this effect. Potassium ions have been shown to have a striking anticurare action (9); ether, in anesthetic concentrations, has recently been found to increase the response of striated muscle to potassium in a small degree, although higher concentrations of ether depress the response to potassium (10). The incidence of respiratory depression caused by curare when used in conjunction with ether anesthesia is understandably high. Curare probably cannot be as safely used in ether anesthesia as with cyclopropane; certainly it should be used with caution, and in smaller doses when any one of the substances mentioned is the anesthetic agent.

A note of warning would not be amiss at this point for those who administer curare to a patient receiving pentothal. In the first place, as

has been described, pentothal has a slight curariform action of its own. Secondly, two respiratory depressants are being used simultaneously. Finally, if the same intravenous needle is used for the administration of both agents, probably a common procedure, a precipitate is formed, which is always produced when pentothal is added to an excess of curare (intocostrin or d-tubocurarine chloride), which conditions are present when curare is given in this manner; the precipitate seems to be soluble in an excess of pentothal solution and possibly in plasma, and appears to be precipitated pentothal.

At the beginning, curare was used largely here in biliary surgery, as the time involved in these procedures seemed nicely fitted to a study of this drug, while the unusual degree of relaxation required in these operations furnished a splendid test of its powers. It was also used in patients undergoing general anesthesia whenever relaxation was necessary and some contraindication for the use of spinal block was present. It was used, also, when abdominal muscle tension returned three hours or more after spinal block had been performed with a long acting drug, again in conjunction with general anesthesia. The 100 cases selected for study are simply the first cases in which curare was used at this hospital.

OPERATIVE PROCEDURES FOR WHICH RELAXATION WAS OBTAINED BY THE USE OF CURARE

	After Spinal Block	Used Alone	Total
Abdominoperineal resection	1	1	2
Adrenalectomy		1	1
Bile duct exploration	1	5	6
Bile duct exploration and cholecystectomy		9	9
Cholecystectomy		28	28
Cholecystectomy and appendectomy		5	5
Colectomy	1	4	5
Colostomy		6	6
Enterostomy		1	1
Excision of carcinoma of ampulla Vater	1		1
Gastrectomy	12	9	21
Gastrectomy and appendectomy	1		1
Hernioplasty, ventral	1	2	3
Hysterectomy and appendectomy		1	1
Intestinal resection	1		1
Laparotomy		6	6
Pancreatectomy		1	1
Repair perforated ulcer	1	1	2
	20	80	100

The first operation in which curare was administered here for abdominal relaxation was performed on May 4, 1943; the one hundredth such case was done on April 17, 1944. The youngest patient so treated was three years old and weighed 23 pounds. The oldest patient in the

series was 91 years old; the heaviest weighed 222 pounds. The average age was 49.6 years; the average weight, 143.7 pounds. The 100 cases represent 100 different patients. In this connection, it may be mentioned that, in the field of psychiatry, it has been stated that there is no increased tolerance to repeated doses of curare.

Initial doses ranged from 12 to 100 mg.; the average first dose was 73.7 mg. The average initial dose in the first 50 cases was 79.8 mg.; this was reduced in the next 50 cases to 67.6 mg.

A second dose of curare was given when requested by the surgeon, during the operation itself or for closing. It may well be that the drug's effect had worn off some short time before, as the anesthetist may have, in some cases, deepened the anesthesia somewhat as the relaxation decreased, or as the surgeon may have requested additional relaxation some time after abdominal muscle tension had returned. Although this increase in time is not thought to be large, it is pointed out in connection with our findings that the intervals between the first and second doses, in the 42 patients receiving curare from the start and requiring more than one injection, ranged from ten minutes to one hundred seventy-five minutes, and that the average such interval, or measurable duration of the relaxation produced by a single dose of curare, was seventy-four and eight-tenths minutes. This compares favorably with the period of ten to fifteen minutes reported by Griffith and Johnson in their original article. Cases in which only one injection was required had to be omitted from this calculation as it was felt that the interval between this injection and the end of the operation did not express a measure of the duration of relaxation. Almost half of the cases, however, in which curare was received from the start, as will be shown, are given only one injection, no further relaxation being needed even at the time of closure.

While pharmacologic evidence suggests that the excretion of curare is very rapid, and that a physiologic dose may be safely repeated within twenty minutes, animal experiments have shown that the drug may have some cumulative action. Our own experience indicates that adequate relaxation may be obtained by second and subsequent doses smaller than the initial injection. Our most frequent additive dose is 40 mg.; the average second dose administered to the 42 cases requiring more than one injection, and in which curare was used from the start, was 47.6 mg.

Curare was used from the start of the operation in 73 cases. In 31, or 42.4 per cent, of these cases, only one injection was necessary; two doses were used in 32 cases, or 43.8 per cent; three doses were given in 7 cases, or 9.6 per cent; four doses were administered in 3 cases, or 4.1 per cent. No more than four doses were given in any single case in the entire series.

The average total doses given in these cases were as follows: in the cases requiring only one injection, 76.8 mg.; when two injections were

given, 125 mg.; for the patients receiving three injections, 168.6 mg.; for those in which four doses were administered, 180 mg. Total doses ranged from 20 mg. to 240 mg. The average total dose for all patients receiving curare from the beginning of the operation was 110.8 mg.

The relaxation obtained by the use of curare was graded "excellent," "fair," or "poor"; in each case observations were made by the anesthetist; the surgeon's opinion was invariably requested, however, and it was his grade that was always assigned to the drug's efficiency. The relaxation was excellent in 92 of the 100 cases and considered fair in 6 cases. It was marked poor in two cases; these operations were done on two consecutive days near the beginning of the series and are numbered 16 and 18 in order of time, so that no "poor" rating was noted for any one of the following 82 cases. It is felt that with increased experience and familiarity with the use of the drug, and with improved technic of dosage and accompanying anesthesia, very few failures to obtain complete relaxation should result.

When respiratory depression was encountered, cases were divided into three groups, according to the severity of the depression: total apnea; depression short of apnea but severe enough to warrant interference on the part of the anesthetist; and mild degrees of depression, to include all slight alterations of respirations, not serious enough to require treatment.

No effect on the respirations was noted in 64 of the 100 cases. Mild depression was seen in 24 cases. Severe depression without actual apnea occurred in 8 cases. Apnea was seen in 4 cases. Thus, in 12 of the 100 cases, artificial respiration had to be instituted, while no antidotal treatment was necessary in 88 per cent of the cases.

In the entire series, there were no deaths attributable to curare, and no harmful after-effects.

CONCLUSIONS

From a study of these cases, it appears that curare can be used by a competent anesthetist in almost every case. It will produce abdominal muscle relaxation during cyclopropane anesthesia at any time without the difficulty, delay, or the complications of spinal block. Its only known complication is easily-treated respiratory depression. In the anesthetized patient, it can produce the so-called "spinal belly" as well as spinal block itself, but it is not a universal substitute for spinal block. In the hands of a trained anesthetist, who is able to perform artificial respiration, the rare myasthenia gravis is curare's only known contraindication.

Curare is believed to be of value in the treatment of laryngospasm, in endotracheal intubation, in esophagoscopy, and in bronchoscopy (where it has been used with and without general anesthesia).

Different viewpoints are held by various investigators with regard to the place curare is to occupy in modern anesthesia. We are con-

tinuing to use it as indicated. At least one prominent worker uses it for almost all abdominal surgery; another (11) restricts its use to cases in which it is really needed, maintaining that inadequate relaxation should be infrequently met and that curare is still a dangerous drug, not to be used indiscriminately by unskilled anesthetists. Thus, it may be used to permit a deliberate lightening of the plane of anesthesia throughout the operation, or it may be given during the course of cyclopropane anesthesia when the required relaxation cannot otherwise be as conveniently secured. Used in the former manner, it may permit the use of cyclopropane with fewer pulse irregularities, because of the smaller blood cyclopropane concentrations maintained. While the exact and complete pathologic change produced by curare is not yet known, most investigators seem to agree that curare appears fairly certain to occupy a lasting place in the pharmacopeia of anesthesia. Cyclopropane-curare combined anesthesia may well become the method of choice for abdominal surgery.

Since submitting this article for publication, curare has been used in 332 additional operations. In some of the cases not included in this series, it was used in conjunction with ethyl ether, pentothal, ethylene and local analgesia.

SUMMARY

1. 158 intravenous injections of curare were given to obtain relaxation in 100 abdominal surgical procedures.

2. Single doses varied from 8 mg. to 100 mg.; the largest total dose used was 240 mg.

3. Excellent relaxation was produced in 92 cases.

4. Severe respiratory depression occurred in 12 cases.

5. No other harmful effects were observed; the circulatory system appeared to be unaffected by therapeutic doses.

6. When respiratory depression occurred, it was always easily treated by artificial respiration.

7. There were no fatalities attributable to curare.

8. The average interval between the first and second doses in cases requiring more than one dose, when curare was used from the start, was seventy-four and eight tenths minutes.

9. In 42.4 per cent of the cases in which curare was used from the start, the relaxation obtained from the initial injection persisted throughout the whole operation and was adequate for closure, so that a second injection was not needed.

REFERENCES

1. E. R. Squibb and Sons: Intocostrin, 1943.
2. Hoffmann, F. A.: Ein Fall von Tetanus Traumaticus mit Curare Behandelt, Berl. klin. Wchnschr. 16: 637–638 (Oct. 27) 1879.
3. Hoche, A.: Versuche mit Curarin bei Tetanie, Neurol. Centralbl. 13: 289–296 (Apr. 15) 1894.

4. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J.A.M.A. 114: 322–324 (Jan. 27) 1940.
5. Griffith, H. R., and Johnson, G. E.: The Use of Curare in General Anesthesia, Anesthesiology 3: 418–420 (July) 1942.
6. Cullen, S. C.: The Use of Curare for the Improvement of Abdominal Muscle Relaxation During Inhalation Anesthesia, Surgery 14: 261–266 (Aug.) 1943.
7. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Co., 1942, pp. 495–498.
8. Gross, E. G., and Cullen, S. C.: The Effects of Anesthetic Agents on Muscular Contraction, J. Pharmacol. & Exper. Therap. 78: 358–365 (Aug.) 1943.
9. Wilson, A. T., and Wright, S.: Anti-Curare Action of Potassium and Other Substances, Quart. J. Exper. Physiol. 26: 127–139 (Oct.) 1936.
10. Torda, Clara: Effect of Chloroform and Ether on Striated Muscle, Anesth. & Analg. 23: 74–77 (Mar.–Apr.) 1944.
11. Griffith, H. R.: The Use of Curare in Anesthesia and for Other Clinical Purposes, Canad. M. A. J. 50: 144–146 (Feb.) 1944.

RESOLUTION ON FORMATION OF ANESTHESIA STUDY COMMISSIONS BY THE AMERICAN MEDICAL ASSOCIATION

Major Harold F. Bishop, Washington, D. C., offered a resolution at the business session of the Section on Anesthesiology of the American Medical Association that the matter of Anesthesia Study Commissions and their importance be presented to the House of Delegates with a view to possible adoption in the educational program of the American Medical Association so that it could be put on a national scale. After discussion, the Section decided that the Chairman appoint a committee of three to consider this matter and present it at the next business session. Major Bishop, Dr. Frederick P. Haugen, and Dr. R. J. Whitacre were appointed to meet with the Executive Committee concerning this resolution. At the next Section meeting, Major Bishop presented the following resolution as drawn up by the committee, which resolution was adopted by the Section, after which it was presented to the House of Delegates of the American Medical Association by Dr. Henry S. Ruth, Section representative, and adopted on motion of Dr. Ruth, seconded by Dr. F. Leslie Sullivan of New York. The resolution reads:

Whereas, There has been introduced a variety of anesthetic drugs and methods during recent years; and

Whereas, A more rapid and accurate method of evaluating these new anesthetic practices is desirable; and

Whereas, There is accumulating evidence that misinformation exists concerning safe administration of anesthetic drugs; and

Whereas, It has been demonstrated that anesthesia study commissions are of educational value to the medical profession; now therefore be it

Resolved, That the American Medical Association should encourage the formation of anesthesia study commissions within the state, county and other similar medical societies.