MYTOLON CHLORIDE: A NEW AGENT FOR PRODUCING MUSCULAR RELAXATION

Preliminary Report * †

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It is probable that few anesthesiologists would disagree with the proposition that the use of agents which interrupt neuromuscular transmission for the purpose of producing relaxation during surgical operations represents the most important advance in the technic of anesthesia during the past decade. Ever since Griffith and Johnson (1) and Cullen (2) demonstrated the value of curare for this purpose, the search has been proceeding for a synthetic substance which might duplicate the effect of that drug with respect to skeletal muscle and yet lack some of its undesirable characteristics.

Pharmacologic Data

It is the purpose of the present communication to describe our clinical experience with a new compound, 2,5-*bis*-(3-diethylaminopropylamino)-benzoquinone-*bis*-(benzyl chloride) (fig. 1) recently synthesized and reported by Cavallito, Soria and Hoppe (3). This substance, designated mytolon chloride, is a red crystalline solid, soluble in water at least to the extent of 20 per cent. The preparation used in this study is an aqueous solution, each cubic centimeter of which contains 3.0 mg. of mytolon chloride. It conforms with the hypothesis regarding curariform activity proposed by Barlow and Ing (4), in that the distance between the two quaternary nitrogen atoms is about 14 angstrom units.

Pharmacologic investigation of mytolon chloride has been reported by Hoppe (5). Curariform activity is exhibited when the drug is administered by the oral, subcutaneous or intravenous route. As has been reported in the case of d-tubocurarine chloride, the curari-

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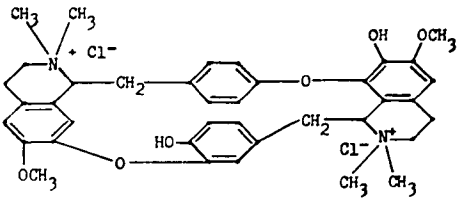
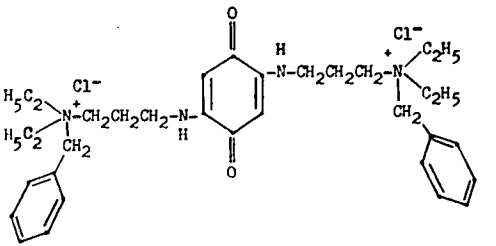


N ←– – – – 13-15 Å – – – – → N

d-Tubocurarine



N ←– – – – 14 Å – – – – → N

WIN 2747

FIG. 1.

metric potency and the toxicity of mytolon chloride vary considerably, depending upon the species of experimental animal to which it is administered. It may be stated in general that the potency equals or exceeds that of *d*-tubocurarine chloride while with equipotent doses the toxicity equals or is less than that of the latter drug. Curarizing doses do not cause any significant change in pulse rate or blood pressure. The drug appears to be without direct cardiac toxicity since 1500 times the curarizing dose could be administered to dogs receiving artificial respiration without causing cardiac arrest. The vasodepressor response is not inhibited by mytolon chloride. In the dog nerve-muscle preparation the dose which causes respiratory arrest is usually identical with that which produces complete arrest of neuromuscular transmission. No effect upon autonomic ganglions or upon the vagus was demonstrated.

METHOD

The clinical observations to be reported were made on 250 surgical patients from the ward and private services at the Massachusetts Memorial Hospitals. The patients were entirely unselected, since mytolon chloride was the agent chosen for all cases in which a muscle relaxant was used. There were 85 males and 165 females in the group. The eldest patient was 81 years and the youngest, 4 years of age. The types of operations performed are shown in table 1.

TABLE 1

TYPES OF OPERATIONS

Upper abdominal operations		32
Cholecystectomy	11	
Gastric operations	13	
Resection or gastroenterostomy with or without vagectomy		
Other operations	8	
Lower abdominal operations		56
Gynecologic	32	
Intestinal resection	9	
Other operations	15	
Thoracic operations		22
Lobectomy or pneumonectomy	4	
Transthoracic splanchnicectomy	6	
Exploratory thoracotomy	7	
Other operations	5	
Lumbodorsal splanchnicectomy		60
Miscellaneous		81
Total		251

Approximately one-third of the operations were laparotomies, and about the same proportion were thoracic operations and lumbodorsal splanchnicectomies. In the group of miscellaneous operations the muscle relaxant usually was administered primarily to facilitate intubation, and in most cases maintenance was satisfactory without its subsequent use. Surgical procedures in this group included thyroidectomy, plastic operations about the head and neck, oral and dental operations, esophagoscopy and laminectomy.

Preoperative medication consisting of demerol or morphine and scopolamine or atropine was administered to all patients. In most cases anesthesia was induced by the intravenous injection of sodium pentobarbital combined with mytolon chloride. Agents used alone or in combination for maintenance were thiopental, hexobarbital, cyclopropane, ether, nitrous oxide and ethylene. Tracheal intubation was performed in approximately 95 per cent of cases.

The most satisfactory technic for the management of the individual case is as follows: after thorough topical anesthetization of the pharynx and larynx by spraying with a 2 per cent solution of pontocaine, induction is accomplished by injecting from the same syringe a combination of sodium pentobarbital, mytolon chloride and atropine sulfate, ad-

ministered during a period of about two minutes. After waiting three to five minutes, anesthesia with the maintenance agent is begun. We have given mytolon chloride without sodium pentobarbital or some other sleep-producing agent in only a few cases because we believe that the sensation of advancing paralysis is disturbing to the majority of conscious patients. Atropine is added to reduce salivary secretions and for its depressing action upon the vagus nerve.

Dosage

The dose of mytolon chloride varies with the physical state of the patient, the type of manipulation contemplated and the anesthetic agent to be employed. For tracheal intubation it is necessary to give 4.5 to 9 mg. depending upon the physical state of the patient, no matter what anesthetic agent is to be used (table 2). If following doses

TABLE 2

Agent	Initial Dose			Start Major Agent	Intubation	Maximal Effect	Maintenance	
	Sodium Nembutal, mg.	Win 2747,	Atropine, mg.				Dose, mg.	Time Interval
Ether	45–120	4.5–9	0.45–0.6	After 3 min.	After 7–10 min.	12–20 min.	3	30 min.
Cyclopropane	60–120	6–9	0.6	After 3 min.	After 7 min.	12–20 min.	4.5–6	20–30 min.
Barbiturate Evipal or thiopental	120	6–9	0.6	After 5 min.	After 7 min.	12–20 min.	6	20–30 min.

are administered only when additional relaxation is required, as recommended by Harris and Dripps (6) for decamethonium bromide, the maintenance dose is 3 to 6 mg. A more satisfactory method is to maintain consistent curarization by regularly spaced doses. When this is done the dose with thiopental or cyclopropane is 4.5 to 6 mg. every twenty to thirty minutes; with ether anesthesia, 3 mg. every thirty to forty minutes.

The initial dose is usually adequate for abdominal operations lasting one hour or less. The largest total doses were 60 mg. administered in combination with hexobarbital during a Wertheim operation of three and one-half hours' duration, and 50 mg. combined with cyclopropane for a pelvic exenteration which lasted five hours. The total dose in comparable operations when ether was used was 20 to 35 mg.

DURATION

It is difficult to determine definite time relationships for the effect of myoneural blocking agents in anesthetized patients. The speed of onset with mytolon chloride is comparable to that with d-tubocurarine chloride, and considerably less rapid than that with decamethonium bromide. Muscular relaxation is noticeable within three minutes after

injection, is marked after seven minutes and maximal for a given dose in from twelve to fifteen minutes. The effect apparently begins to recede soon after reaching its peak. When apnea occurs it is of short duration. No period of apnea has exceeded fifteen minutes unless an additional dose of mytolon chloride was given.

On three occasions the drug has been administered without any premedication or anesthesia to conscious young men in doses of 6 mg., 7.5 mg. and 9 mg., respectively. In each case the duration and time relationships were the same as those in anesthetized patients. In conscious individuals the effect of the drug had entirely disappeared at the end of the forty minutes.

EFFECT ON RESPIRATION

When mytolon chloride is administered in amounts sufficient to produce relaxation of skeletal muscle adequate for intubation or abdominal exploration under light anesthesia, it causes definite respiratory depression. The extent of the depression is related not only to the size of the dose but also to the anesthetic agent. The intercostal muscles are affected earlier and by smaller doses than is the diaphragm. When the anesthetic agent is a barbiturate (hexobarbital or thiopental) the depression is likely to be more marked and of longer duration with a given dose of mytolon chloride than when ether or one of the gases is being used. The depression is usually characterized more by a decrease in amplitude than by any change in character, rate, or rhythm, no matter what anesthetic agent is involved. The jerky, spasmodic type of respiratory effort is rarely seen with mytolon chloride.

In our series, there has been no instance of prolonged respiratory depression. In all cases ventilation has been adequate when the mask was removed at the conclusion of the operation. Patients in whom breathing is purposely maintained with controlled respirations promptly resume spontaneous breathing when the intermittent bag pressure is changed so as to "assist" rather than "control."

When the drug was administered to the conscious patients, previously described, a decrease in intercostal activity occurred in all 3, beginning in three minutes and appearing most marked at ten to twelve minutes. There was no instance of diaphragmatic paralysis in conscious individuals with doses up to 9 mg.

There has been no evidence of bronchoconstriction at any time following injection of mytolon chloride.

EFFECT ON CIRCULATION

The effect of mytolon chloride upon the heart and circulation is difficult to assess when it is administered clinically because the general anesthetic agents and the events incident to the surgical procedure also act upon the cardiovascular system. No changes in pulse rate or

rhythm have been observed following the injection of the drug. When the muscle relaxing agent is administered intravenously along with any barbiturate, either sodium pentobarbital, thiopental or hexobarbital, moderate falls in blood pressure occur in some cases. This happens no more frequently with the muscle relaxant than when the intravenous barbiturate is used alone. In a few cases, when mytolon chloride was administered alone, there has been a momentary fall in blood pressure of the order of 10 to 15 mm. of mercury during injection followed by an immediate rise to, or slightly above, the original level. When mytolon chloride is injected after anesthesia is already established, there is either no change or a slight rise in both systolic and diastolic blood pressure levels. On two occasions this drug was administered to facilitate closure at the end of a long operation when spinal anesthesia had receded. No change in blood pressure occurred in either of these instances.

Mytolon chloride was administered to 60 hypertensive patients undergoing lumbodorsal splanchnicectomy. No deleterious effects were observed. In fact, it was our clinical impression that blood pressure levels were maintained during operation more satisfactorily in the patients who received the agent than in those who did not, probably because it was possible to maintain anesthesia at a slightly lighter plane.

MUSCULAR RELAXATION

Administered in adequate amounts, mytolon chloride is capable of effecting complete myoneural block and muscular flaccidity. The degree of relaxation provided is indistinguishable clinically from that of d-tubocurarine chloride or decamethonium bromide when the agents are administered in comparable doses. The dose necessary to produce relaxation adequate for abdominal operations is approximately twice as large with thiopental, hexobarbital or cyclopropane as when ether is used. Respiratory depression is less marked when comparable degrees of relaxation are obtained during ether or cyclopropane anesthesia than when thiopental or hexobarbital is the agent. With cyclopropane or a barbiturate as the anesthetic agent, the intestine is well collapsed and retracted. This is not true in so great a degree with ether. Experimentally, mytolon chloride was shown to have slight stimulatory or no effect upon intestinal motility (5).

OTHER SIDE EFFECTS

In several cases early in the study when mytolon chloride was administered without the addition of atropine sulfate, excessive salivation was an annoying complication. This was especially troublesome if any manipulation such as intubation was undertaken early. Since the procedure has been modified by injecting 0.4 to 0.6 mg. of atropine sulfate along with the muscle relaxant and postponing manipulation

for five to seven minutes after injection we have not had this difficulty with secretions. It is interesting that increased salivation did not occur when mytolon chloride was administered to conscious individuals in amounts up to 9 mg. Each conscious patient who received the drug, however, noted dizziness within one minute after injection. There was no drowsiness or loss of consciousness. One patient noted tingling in the extremities and one stated that he could not swallow. Observations of the effect of the drug in conscious patients are being continued and will be reported in a later communication.

POSTOPERATIVE COURSE

Recovery from anesthesia was not prolonged following the use of mytolon chloride. It appeared that with the inhalation agents, emergence was actually hastened since closure of the wound could be accomplished in a superficial plane of anesthesia. All patients were capable of moving their extremities and moving about in bed as soon as they were sufficiently conscious to comprehend requests to do so.

EXCRETION

Mytolon chloride is excreted in the urine. When administered to dogs by continuous infusion, approximately 65 per cent of the drug was eliminated during the course of the experiment. Following large doses the urine of the patient was colored red, the color of the compound.

COMMENT

In addition to the agents derived from curare, several synthetic compounds are now available which are capable of producing a block of the myoneural junction with resulting relaxation of skeletal musculature. These agents differ in important respects from curare and from each other. It follows, as Unna, Pelikan and associates (7) pointed out, that they should not be selected simply as alternatives to d-tubocurarine. They should be employed for their own merits to accomplish a definite objective. In other words, perhaps we now have a sufficient variety of these agents to be able to select them for definite indications: for example, d-tubocurarine because in addition to producing muscle relaxation it depresses certain dangerous reflexes (8), or decamethonium bromide, because its effect is evanescent and it is relatively free from histamine-like effects.

Before mytolon chloride can be completely evaluated further investigation is necessary, particularly in regard to its effects on unanesthetized human subjects. Judging from the laboratory reports and from our clinical experience to date, its chief advantages are its lack of effect upon the cardiovascular system and the prompt recession of respiratory depression following its use.

An interesting observation concerns the difference in muscular relaxation as related to the severity of respiratory depression when different anesthetic agents are used. As has previously been stated, ether has a definite potentiating effect upon mytolon chloride and maintenance doses with that agent are approximately half those necessary with cyclopropane or thiopental. In the presence of adequate muscular relaxation for intubation or for abdominal work, however, respiratory depression is less severe and complete apnea less frequent when ether is used. Respiratory effects are somewhat more marked with cyclopropane, and most severe and prolonged with thiopental. In a few patients receiving thiopental the abdominal muscles were not satisfactorily relaxed although respiratory activity was completely paralyzed. While the so-called "curarizing effect" of ether is no doubt the chief factor in the potentiation of mytolon chloride, these observations seem to indicate that other considerations are involved. Actually, it is probably the case that adequate "curarization" under clinical conditions is not a complete myoneural block. It is known that increasing the strength of the stimulus will bring about contraction of partially curarized muscles, and that summation (Wedensky facilitation) will result in contraction if two successive stimuli of sufficient strength are applied to the motor nerve of a curarized muscle (9, 10). In the course of an abdominal operation proprioceptive tonus is brought into play by traction on muscles, and protective flexion reflexes are stimulated by the pain incident to the manipulation of the peritoneum and mesentery. Afferent impulses originating in this way are more effectively interrupted by ether or cyclopropane than by thiopental and it may be postulated that the summation of stimuli which would result in contraction of partially curarized muscle thus is prevented. On the other hand, at comparable levels of anesthesia, thiopental produces a greater degree of central respiratory depression than do the inhalation agents. Hence, in the case of thiopental, the impulses transmitted over the motor nerves to the respiratory muscles may be inadequate to evoke a contraction across the myoneural block.

SUMMARY

Mytolon chloride was administered to 250 unselected patients for the purpose of producing muscular relaxation during operation.

This agent interrupts the transmission of motor impulses at the myoneural junction, and the degree of flaccidity produced depends upon the amount administered.

No evidence of deleterious effect upon the cardiovascular system was noted in this series of observations.

Mytolon chloride does not affect transmission of autonomic impulses.

No histamine-like effects have been observed.

Mytolon chloride is an efficient agent for the production of muscular relaxation during surgical procedures. In view of the characteristics previously stated, it is recommended for further clinical trial.

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