CLINICAL AND LABORATORY OBSERVATIONS ON THE USE OF CURARE DURING INHALATION ANESTHESIA * †

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INTRODUCTION

MANIPULATIONS within the abdomen are always facilitated by a state of complete muscular relaxation, associated with quiet breathing and contraction of the intestine. If this state can be achieved without increased hazard to the patient during anesthesia or without predisposing toward undesirable sequelae, the convenience to the surgeon expedites his work and directly contributes to a smoother, more complete, and more rapid convalescence of the patient. There are certain inadequacies in the ability of present day anesthetic agents and technics to provide this optimal state, with the result that many situations arise in which the patient is subjected to near lethal ranges of agents and technics, the surgeon is frustrated, and the anesthesiologist is embarrassed. Curare is proposed, not as a panacea, but as another adjunct to anesthetic drugs and methods in an attempt to secure safer anesthesia for the patient, better working conditions for the surgeon, and more peace of mind for the anesthetist.

In the analysis of the material to be presented, it will be well to keep in mind that the technic described is that best suited to the requirements of the patients and surgeons in our locale. From this exposition, it is expected that some knowledge of the action of curare will be gained and only one manner of applying it during inhalation anesthesia will be learned. Furthermore, it is emphasized now and later that the relaxation obtained with curare should not and cannot be a substitute for imperfect working conditions associated with poorly conducted inhalation anesthesia.

A few of the inadequacies of current agents and technics used for anesthesia for intra-abdominal surgery are listed.

Ether is capable of producing extreme muscular relaxation, but this relaxation is accompanied by acidosis, hemoconcentration, and glycogenolysis. In addition, the abdomen is over-active from accentuation of the diaphragmatic movements and the intestines are not contracted and

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are difficult to confine. This is followed by a prolonged postanesthetic recovery period, with nausea and emesis, distention, and a universal debility which predisposes toward pulmonary complications. Cyclopropane will produce a moderately contracted intestine and a quiet abdomen, but, alone, it is incapable, with voluntary respiration, of supplying complete muscular relaxation in most persons. By means of controlled respiration, the relaxation can be improved. This technic, however, introduces possibilities of trauma, even in experienced hands. Although apparently of little or no practical significance, this technic reverses the intrathoracic cardiorespiratory dynamics. Complementing cyclopropane anesthesia with intercostal nerve or abdominal wall block provides, in most cases, optimum working conditions in the abdomen, but the blocks are not completely dependable and increase the time of complete induction of anesthesia. Prolonged, high concentrations of cyclopropane seem also to predispose to arrhythmia and to postanesthetic primary hypotension.

Nitrous oxide is usually unable to produce satisfactory anesthesia for intra-abdominal procedures unless accompanied by asphyxia or complemented with block. In occasional, poor-risk patients, with lax and thin abdominal walls, it is able to produce good anesthesia with abdominal wall or intercostal block. Ethylene is similar to nitrous oxide in its ability to produce relaxation and a quiet abdomen, but it will be sufficient in only a few more cases than nitrous oxide. It is usually necessary to add ether, cyclopropane or nerve block.

Although not recommended by the prudent anesthesiologist, barbiturates introduced intravenously can be employed for anesthesia for intra-abdominal surgical procedures. They are capable of providing excellent relaxation, quiet breathing, and a contracted intestine. They predispose, however, toward reflex laryngospasm and prolonged postanesthetic recovery. Their use in upper abdominal manipulations is particularly hazardous. These drugs are occasionally employed to provide momentary relaxation during inhalation anesthesia by other agents. Even though barbiturates are used relatively sparingly and intermittently throughout inhalation anesthesia, the development of severe laryngospasm or bronchospasm is a real and ever present menace.

Intrathecal block will, when properly managed, result in optimal working conditions for abdominal procedures. The patient, however, is frequently uncomfortable because of nausea, the long sustained, unaltered position, and the incompletely suppressed sense of traction and pressure. It is beginning to be common practice to complement spinal anesthesia with inhalation or intravenous barbiturate anesthesia. This practice could be interpreted as a tacit admission that the patient is not comfortable under spinal block alone. In addition, the circulation is often disturbed, and, although it can be controlled in most instances, its alterations are evidence of serious interference with the patient's compensatory mechanisms. Occasional, though fortunately infrequent,

neurological sequelae of intrathecal block are to be reckoned with in a consideration of choice of anesthetic technics.

It is apparent that recognized anesthetic agents and technics fail to fulfill completely the requirements of good anesthesia for abdominal operations, namely, (1) maximum comfort for the patient, (2) maximum safety for the patient, and (3) maximum convenience for the surgeon. In an effort to approximate the ideal state more closely, curare is being used to improve abdominal muscle relaxation and contract the intestine during inhalation anesthesia.

HISTORY AND PHARMACOLOGY OF CURARE

The popular concept that the principal usefulness of curare is to paralyze the game of foraging South American Indians or to perform experiments in the pharmacology laboratory is gradually being displaced by a succession of interesting and valuable clinical applications. Since 1857, it has been used practically in the treatment of convulsive states, such as tetany, strychnine poisoning, and chorea (1). It has also been advocated for the control of muscle spasm in spastic disorders (2). It is now in common use as a means of reducing the violence of the convulsions associated with metrazol or electric shock therapy (3).

The drug is obtained from an extract of the bark, vines, and leaves of several species of plants. Because of the fact that some of the extracts produce centrally excited convulsions, the drug was early assumed to be related to strychnine, and some of the species were named *Strychnos toxifera.* The South American Indians have long been aware of the properties of this drug, and it has been intimately associated with their livelihood and witchcraft for centuries. It was first brought to civilization in the latter part of the sixteenth century by Sir Walter Raleigh. It was investigated pharmacologically by Pelouze and Bernard (4) in 1850, and they demonstrated then the as yet unrefuted fact that curare kills only by asphyxia accompanying respiratory paralysis. Its introduction in quantity to this country is in large measure due to the efforts of Richard Gill (5). He was intrigued with the clinical possibilities of "the flying death," and spent many years among the Ecuadorian Indians learning the secret of its extraction and obtaining many botanical specimens. Its chemical and botanical development in this country was the result chiefly of the efforts of the members of the research organization of E. R. Squibb and Sons Company and Dr. McIntyre of the University of Nebraska. The commercial extract (intocostrin—Squibb) is obtained from *Chondrodendron tomentosum.* This plant produces a drug which is free from the undesirable side effects that are present in the extracts from other species.

Although Gill maintains that it is a pure coincidence of Indian witchcraft, curare is known to exist in three forms which are named for the type of packaging. It may be known as tubocurare because it comes in bamboo tubes. The active principles of this form are said to be tubo-

curarine and curine. It is known as calabash curare because it comes in gourds. The active principle of this form is said to be curarine. It is also known as pot curare because it comes in earthenware pots and its active principle is said to be protocurarine.

The principal mechanism of action of curare is the blocking of the response to the nicotinic action of acetylcholine. It not only prevents the effector substance of voluntary muscle from reacting to acetylcholine, but it also quite effectively blocks synaptic transmission between preganglionic and postganglionic fibers of the sympathetic division of the autonomic nervous system. Its action does not extend to structures innervated by postganglionic fibers, such as glands and smooth muscle. There is evidence that curare blocks peripheral response to vagal stimulation (6). Its action is predominantly peripheral, although a central depression of respiration has been reported (7). Choline esters, physostigmine, and prostigmin are antagonistic to the action of curare, probably because they permit the acetylcholine to act longer or in a higher concentration. There is no apparent limitation of production of acetylcholine. Reduction of blood levels of cholinesterase by curare has been reported (8). This cannot, however, be interpreted as a reduction of cholinesterase activity at the end plate.

Curare is partially destroyed in the liver and partly eliminated unchanged by the kidneys. No evidence has been encountered which tends to show that liver or kidney impairment prolongs or intensifies the action of curare. No direct effect on the heart is reported. Electrocardiographic tracings of normal and abnormal human hearts fail to show any influence of the administration of therapeutic amounts of curare (9). Large amounts given intravenously in a short period of time occasionally produce a momentary fall in blood pressure. Long-continued administration will also reduce the blood pressure level (10), but this may be the result of impaired venous return accompanying the widespread peripheral muscle relaxation.

Curare is selective in action, and affects the muscles of the head and neck before progressing to the muscles of the extremities and abdomen and ultimately to those of respiration. The diaphragm is the last muscle to be affected. No analgesic action has been demonstrated. Its effect, when given intravenously, is obtained within two minutes, and when given intramuscularly, is obtained within fifteen minutes. It is not effective when administered perorally or subcutaneously, probably because absorption is so slow that an effective blood level is not reached. Its action persists for twenty minutes, and there is apparently little or no cumulative effect on repetition of the drug within an hour or two. Overdose causes respiratory paralysis, from which recovery is complete if artificial ventilation of the lungs with oxygen is maintained during the paresis. No temporary or permanent organic damage has as yet been demonstrated following the use of curare.

Curare is supplied as an extract, standardized by biological assay to contain the equivalent of 0.02 Gm. per cubic centimeter of a standard drug. The biological assay for this drug is, fortunately, one of the most reliable and consistent methods of assay available.

The inhalation anesthetic procedure during which curare is employed is not altered in any significant particular. Premedication is of the same nature and dosage as ordinarily used. It appears, however, that atropine or scopolamine is essential in the premedication. In 1940, when the use of curare was first considered as an adjunct to inhalation anesthesia, several dogs which were unpremedicated were given relatively large doses of the drug. They salivated profusely, had marked respiratory difficulty, cyanosis, and muscular twitchings. These reactions were duplicated later in the case of a woman, who was also unpremedicated, to whom curare was given in an attempt to obtain muscular relaxation for a bimanual pelvic examination. In the woman, the intravenous administration of morphine and scopolamine promptly restored efficient respiration. This effect has not been duplicated in subsequent studies of the action of curare on laboratory animals. It may be that it is necessary to block out the muscarinic action of acetylcholine by atropine or scopolamine. Psychiatrists are not using atropine as premedication, but the doses they employ are smaller than those used in anesthesia.

The induction and establishment of anesthesia are performed as usual with the carbon dioxide absorption technic. If curare is applied in the manner Griffith (11) recommends, it is used only in those situations in which it is impossible or too hazardous to obtain relaxation with the anesthetic agent alone. In this circumstance the curare is administered intravenously. Usually, 0.100 Gm. (5 cc. of intocostrin) is required in the average sthenic patient under cyclopropane anesthesia. It is our practice to use curare more freely, and obtain relaxation with it, rather than to increase the concentration of the anesthetic agent to obtain relaxation. It is possible to carry the patient in light second plane inhalation anesthesia, and, with proper doses of curare, obtain as good relaxation, contraction of the intestine, and quiet breathing as with spinal anesthesia.

Accordingly, in those intra-abdominal procedures in which relaxation and contraction of the intestine are desired, the anesthesia is leveled off in the second plane. When the abdominal preparation or skin incision is made, the curare is introduced intravenously, and, by the time the peritoneum is opened, the maximum effect of the initial dose is obtained. Most adults in good health will tolerate at least 0.060 Gm. as an initial dose. If this proves insufficient, one-half to two-thirds of the initial dose is added after three to five minutes. To this may be added smaller quantities until the optimal state of quiet breathing, complete relaxation, and contraction of the intestine is attained. Once attained, this state usually can be maintained until closure of the abdomen. It is rarely

necessary to add curare during long operations, but, if the procedure lasts longer than forty-five minutes, it is usually necessary to add one-half to two-thirds of the initial dose to facilitate closure of the peritoneum.

The amount of drug necessary to produce the ideal state often appreciably depresses the respiration. This depression is characterized by complete intercostal paresis and shallow, jerky movements of the diaphragm. The depression lasts only about five minutes. In twenty-four of the 800 cases in which curare has been used, complete respiratory paresis developed, but it persisted only two to five minutes, and there was rather quick return to effective minute-volume exchange. Since it was so effortless and efficient, artificial ventilation by manual compression of the rebreathing bag was all that was used for treatment. It was necessary to use prostigmin in but one case. Ether was the anesthetic agent in this case.

The agent most frequently used is cyclopropane. With this agent there is no excessive or prolonged respiratory depression with optimal doses of curare. The optimal state can be achieved with relative ease and the patient allowed the benefit of a pleasant induction, a quick recovery, and minimal postanesthetic discomfort. An investigation of the effect of curare on the heart in animals anesthetized with cyclopropane is now in progress. Clinical experience leads us to believe that curare does not potentiate the cardiac irregularities produced by cyclopropane, and may afford some protection. If cardiac irregularities during cyclopropane anesthesia are produced by stimulation of a center in the brain stem and transmitted through sympathetic fibers (12), or if they are due to vagal escape phenomena, it is a theoretical possibility that blocking of response to acetylcholine by curare would be beneficial. Under the conditions of our experiments, we could demonstrate that curare neither increased susceptibility of the heart nor offered protection to the action of cyclopropane.

Curare is being used during anesthesia with nitrous oxide, and provides the muscle relaxation not ordinarily secured with this anesthetic agent alone. Curare is also being used during ethylene anesthesia. This agent is somewhat more potent than nitrous oxide and should provide more latitude in depth of anesthesia without asphyxia. It is, of course, non-toxic, and preferable in this respect to cyclopropane. Our experience to date with ethylene demonstrates that it is possible to secure good relaxation and a quiet abdomen, but it is necessary to use larger doses of curare, and respiratory depression is more frequent, more marked, and more prolonged. Although the oxygen concentration in the inspired atmosphere is at least 20 per cent, considerable difficulty with cyanosis has been experienced. Strangely enough, this difficulty was not encountered with nitrous oxide.

It is unnecessary to use curare during anesthesia when the barbiturates are introduced intravenously, because they alone are capable of

producing complete relaxation, quiet breathing, and contraction of the intestine.

Curare can be used during ether anesthesia, but the dose must be reduced to one-third of that used during cyclopropane anesthesia. Experiences gained during the use of curare with ether prompted investigation into the effect of several anesthetic agents on the humoral transmission of nerve impulses (13). The agents studied were cyclopropane, ethylene, ether, tribromethanol with amylene hydrate (avertin fluid), and sodium ethyl (1 methylbutyl) thiobarbiturate (pentothal sodium). It was found that humoral transmission of nerve impulses was not greatly interfered with by cyclopropane and ethylene. In high concentration, but within the anesthetic range, pentothal sodium and avertin fluid produced a moderate amount of interference. Ether had a marked curariform action which, interestingly enough, had been ascribed to it as early as 1914 (14). These studies helped to make clear not only the increased depression which occurs with the concomitant use of ether and curare, but also assisted in elucidating the clinical observation of unequal muscular relaxation during equal levels of anesthesia with cyclopropane and ether. Curare is advantageous during ether anesthesia because relaxation can be obtained without deep anesthesia, but, more significantly, it contracts the intestine and produces a quiet abdomen. The quiet abdomen is not obtained at the expense of efficient pulmonary ventilation.

No postanesthetic complications have been noted which can be either directly or indirectly ascribed to curare. Before the use of curare in combination with cyclopropane, most of the upper abdominal and major lower abdominal operations were done with ether anesthesia. Although figures have not been compiled, there is a distinct clinical impression on the part of surgeons, floor nurses, and anesthetists that postoperative pulmonary complications, distention, retention, and general debility are less frequent since it has been possible to use gaseous agents for this type of surgical procedure.

Experiences with curare during inhalation anesthesia and laboratory investigations of its properties give the impression that curare is a safe drug, and that it is proving to be a valuable adjunct to the anesthetist's armamentarium. Its ability to provide complete muscular relaxation and contract the intestine assists materially in improving the working conditions of the surgeon without significantly increasing the immediate or ultimate hazard to the patient. Its principal disadvantage is the narrow margin between the effective dose and the dose which produces respiratory depression. With proper control of respiration, this disadvantage proves, however, to be minimal. Complete and unqualified recommendation of the drug is withheld pending further clinical and laboratory investigation. It should not be used by the inexperienced and unskilled anesthetist to secure relaxation which is otherwise unobtainable because of inadequate anesthesia. Curare can be used suc-

cessfully and safely only in conjunction with properly conducted inhalation anesthesia.

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COMING EXAMINATIONS

The Part II (Oral) Examinations for certification by the American Board of Anesthesiology, Inc., will be held in Chicago, June 9, 10, and 11, 1944. Paul M. Wood, M.D., 745 Fifth Avenue, New York 22, N. Y., Secy.