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CURARE AS AN AID TO THE ANAESTHETIST

by

HAROLD R. GRIFFITH, M.M., B.A., M.D., C.M.,

HON. WING COMMANDER, CONSULTANT IN ANAESTHESIA,

R.C.A.F., MONTREAL, CANADA.

(From the Department of Anaesthesia,

Homoeopathic Hospital of Montreal.)

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It is now more than three years since we first began to use a purified extract of the old drug curare as a muscle relaxant in patients under general anaesthesia. (1) Numerous reports from anaesthetists throughout the world are confirming our original surmise as to the clinical efficacy and safety of this application of curare. I believe that it is now possible to make at least a preliminary appraisal of the true place of curare in anaesthesiology, and I propose briefly to discuss the drug under the following headings:

1. The need for curare
2. The efficacy of curare
3. The safety of curare
4. The effect of curare on the future practice of anaesthesiology.

1. Need. Every anaesthetist, even the most expert, has wished at times that there was some way in which he could instantly and safely produce complete muscular relaxation in his patient. Muscle relaxation is often a prime requisite for good surgery and to obtain adequate relaxation the anaesthetist may be forced to use anaesthetic drugs, either general or regional, in doses beyond the optimum for the safety and comfort of the patient. It was the need for a drug which would produce controllable relaxation without added toxicity



which led us to experiment with curare in anaesthesia.

2. Efficacy. The purified extract of curare which was introduced into clinical medicine in 1940 by E.R. Squibb & sons of New York under the name of "Intocostrin" was first used in neuro-psychiatry, and its major application before its use in anaesthesia was by Bennett of Nebraska for the minimizing of trauma in patients undergoing convulsive shock therapy. This led us to a cautious trial in patients under cyclopropane anaesthesia, and from the very first patient it became obvious that here was an efficient drug to promote relaxation with few side effects. The dosage and method of administration have varied widely with different investigators. Some anaesthetists, notably Gullen of Iowa, have given curare routinely in all abdominal operations under general anaesthesia, usually by repeated intravenous injections of small doses of 40 to 60 mg. (2 to 3 cc. of "Intocostrin") Knight and Baird of Minneapolis have also reported successful series of administrations using this technique. My own practice has been to administer curare only when there is need to obtain increased muscular relaxation. This may be done at any time during the operation and should be in adequate dosage (60 to 100 mg. for an adult under cyclopropane,) but is by no means necessary in every abdominal case. A recent survey of our own cases shows that, although we now use curare on the slightest provocation, we still are administering it in only 38% of our abdominal operations. Curare should not be made the excuse for a poor anaesthetic sloppily administered.

For many years it has been my own practice to use cyclopropane as the agent of choice for general anaesthesia to the almost complete exclusion of ether. For this reason most of my work with curare has been with patients under cyclopropane anaesthesia. The two drugs seem to make an ideal combination and enable us to obtain at will relaxation similar to that of spinal anaesthesia. Curare may also be used in ether anaesthesia or when ether is combined with cyclopropane, ethylene



or nitrous-oxide, but under these circumstances the dose of curare should be greatly reduced - to an average of 20 to 40 mg. (1 to 2 cc. of "Intecostrin") for an adult. Cullen has shown that ether itself has a curare-like action on the myo-neural junction, which accounts for the greatly enhanced effect of curare in patients under ether anaesthesia. Macintosh, of Oxford, is using small doses of curare successfully in patients under light ether, administering it by continuous sternal drip.

Curare may also be used with other anaesthetic agents. Waters reports satisfactory anaesthesia for upper abdominal surgery using curare in combination with nitrous oxide-oxygen without added ether. I have frequently given curare to patients under ethylene or ethylene-cyclopropane with good results. Incidentally, I would like to interject a good word for that almost forgotten agent, ethylene - a particularly safe anaesthetic for use in such poor risk cases as toxic thyroids, and made doubly efficient when combined with curare.

Hudon, of Quebec, and others have shown how curare may be used to reinforce the action of pentothal. It may be given to patients in whom the relaxation of spinal anaesthesia is wearing off too soon, provided that the sensibility of the patient is well obtunded by hypnotics or a "sleeping dose" of general anaesthesia. It may also be used to facilitate bronchoscopy in muscular patients, and tracheal intubation in cases where there is difficulty in securing adequate relaxation. However, curare in safe doses is not in any sense an anaesthetic agent and I do not recommend it for general use in conscious patients. The effect is too uncomfortable. My own feeling is that curare is most effectively used with gas anaesthetics, especially cyclopropane, and also, but more cautiously, with ether. It may be given intramuscularly without irritation, but we prefer to use it intravenously because of the greater control thus assured.

3. Safety. Perhaps the most surprising outcome of the whole curare investigation is the absence of evidence of toxicity, either immediate or post



operative. It is hard to believe that a drug which has such a fabulous reputation as a poison could be used so safely in clinical medicine. The work of \_\_\_\_\_ and a host of physiologists, both before and since his time, has all been done with a comparatively crude curare of uncertain composition and containing a variable quantity of other adulterating substances.

R.C. Gill, an American who had lived for years in the Amazonian jungles of Ecuador, brought to civilization in 1938 the first botanically identifiable supply of curare and his work made it possible for Prof. A.R. McIntyre of Nebraska, the Research Laboratories of E.R. Squibb & Sons of New York, and others to produce the first pharmacologically standardized extracts of curare. This new product is rapidly broken down in the human body and completely eliminated. When administered intravenously in a simple dose it acts within thirty seconds, maintains its maximum effect for about five or ten minutes and then gradually disappears until its effect is all gone in about twenty minutes. The effect may be prolonged by a judicious combination with whatever anaesthetic agent is being administered simultaneously. This rapidity of elimination from the body is undoubtedly the greatest safety factor in the use of curare in anaesthesia..

The question of what is the optimum dose and what will happen when an overdose is given has been the subject of some interesting recent reports. During anaesthesia the administration of what is considered an average dose of curare will occasionally cause the patient's respiration to become very shallow or to cease. This is because of the paralyzing effect of the drug on the accessory muscles of respiration and finally on the diaphragm. All the treatment that is necessary is to carry on artificial ventilation of the lungs by manual compression of the breathing bag during the few minutes it takes until this depressing curare effect passes off. I have never seen even any temporary damage resulting to the patient. "Prostigmin," a drug which appears to be physiologically antagonistic to curare, has been recommended as an antidote, but personally I have never needed to



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use it. Curare may be given to anemic, frail, or shocked patients apparently without jeopardizing their chances of survival. I have given effective doses on several occasions to patients in almost pulseless condition from ruptured ectopic pregnancies, and there are numerous reports of its efficacy in traumatic surgery. Whitacre, of Cleveland, in a most important recent article, records the results of experiments to determine the effect of very large doses of curare on human subjects. He makes the surprising observation that a single intravenous injection of 200 mg. of curare (10 cc. of "Intocostrin") - or about double the dose I have even used therapeutically - produces sudden unconsciousness, complete muscular relaxation and apnoea. If artificial respiration with adequate oxygenation is then maintained, blood pressure, pulse and circulation are unaffected, but the patient remains unconscious and relaxed. By repeating the injections of curare it has been possible to perform operations such as a gastrectomy, using no other anaesthetic agent. This involves a revolutionary view of the physiological action of curare and is not easily explained, but from the purely clinical viewpoint it is reassuring to know that even such large doses of curare may be given without irreversible effect. During the recovery period Whitacre's patients showed some tendency to bronchospasm, increased bronchial secretion, and other undesirable side effects, so that neither he nor I advocate using curare as a practical method of anaesthesia. We are just glad to know that doses up to 400 mg. have been given to human patients without fatal effect. An even more striking example of an overdose of curare has been reported by Robson of Toronto. His patient was an eight-pound baby, two-weeks old, undergoing operation for a complete diaphragmatic hernia with ether anaesthesia. By mistake a dose of 1 cc. of "Intocostrin" (20 mg. curare) was given intravenously to improve relaxation. This was at least fifteen times the recommended dose for such a patient. There was immediate complete relaxation and also complete cessation of respiration. Dr. Robson cleverly maintained artificial respiration with endotracheal oxygen for more than three hours before there was the



least sign of returning muscular activity. In the meantime, the surgeon had completed the operation under ideal conditions, and eventually the baby recovered without permanent damage. These case histories tend to reassure us regarding the safety of modern extracts of curare, when properly used, but I hope they will not cause us to forget that when improperly used curare is still a poison, capable of producing death by respiratory paralysis.

The only side-effect which we have noted in curare, other than occasional respiratory depression, is a transient bronchospasm which developed in three patients immediately following the intravenous injection of moderate doses. This is recorded as a possible effect of curare, with no suggestion as to the cause - the patients resumed normal breathing within one or two minutes. The preparations of curare we have used "Intocostrin" and the newer extract "d-tubocurarine" are not irritating to the subcutaneous tissues and there has been no case recorded of phlebitis or other similar complication.

4. Effect of curare on the future of anaesthesiology.

Five years ago when it was first suggested to me by Dr. L.H. Wright, of New York, that curare might be useful in anaesthesia, I laughed at the idea. I thought about it for more than a year, and in January, 1942, I tried it out. Since then I have watched its use spread around the world. There is no doubt that it is filling a need. Developments in anaesthesia during recent years have been mainly toward increased safety and comfort for the patient. Here is a drug which allows the surgeon to work more efficiently without increasing the hazard to the patient, a most important objective in surgical progress. It is no wonder that the surgeons are enthusiastic supporters of the use of curare in anaesthesia. I feel now that curare will enable us to use the non-toxic and controllable gas anaesthetic agents, particularly cyclopropane and ethylene in a wider variety of major operations; that it will reduce the use of spinal anaesthesia for upper abdominal surgery with its attendant hazards; and that it will afford more efficient anaesthesia with low



concentrations of ether when that agent is chosen.

Opinions about curare vary all the way from that of a leading anaesthetist who states that "curare bids fair to replace not only a great deal of deep ether anaesthesia but a great deal of spinal anaesthesia as well," to the comment of one medical columnist, "why not learn to give an effective anaesthetic?" Personally I am not venturing to prophecy, but I do know that curare will never take the place of the anaesthetists' skill. The experience, ability and judgment of the anaesthetist is more important than any new agent or method, and I believe that curare should remain as just one more good thing in the modern anaesthetists' bag of tricks. It is not a plaything for the inexperienced.

Summary.

The use of curare in anaesthesia has been reviewed with particular reference to its efficacy and safety as a muscle relaxant in patients under cyclopropane, ether, and other general anaesthetic agents. In the light of more than three years' clinical experience, it is considered to be of value to expert anaesthetists by affording a better surgical field for abdominal operations with light and non-toxic anaesthesia. It will probably have a permanent place in anaesthesiology.



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