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CURARE IN ANAESTHESIA.

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The introduction of curare into clinical medicine has provided the anaesthetist with a most useful new tool. To be able to produce complete muscular relaxation quickly and safely at any time during the course of an operation is a goal of which every anaesthetist and surgeon has dreamed. Rigid abdominal muscles are the cause of more profanity by the surgeons and sweat and tears by the anaesthetists than any other occurrence in the operating room. Curare, the old familiar plaything of the physiological laboratory, will give us this desired relaxation, and after more than two years of clinical experimentation, those of us who have been using it in the operating room have concluded that it is quite safe when administered under properly controlled conditions.

The story of the transformation of this South American Indian arrow poison into an anaesthetist's tool may be told briefly as follows: Curare has been known to science since 1595 when Hakluyt referred to it in his description of Sir Walter Raleigh's voyage up the Orinoco. In 1840 Claude Bernard, (1) in a series of famous physiological experiments, confirmed the observations which Watterton and Brodie had made in 1814, that curare action was paralysis due to interruption of neuro-muscular mechanism. The drug therefore became of value in the physiological laboratory for the study of muscle activity without interference from nervous impulses. Clinicians had more than once cast hopeful eyes toward the possible use of curare in the treatment of spastic disease of the muscles but always its poisonous reputation and the presence of cardiac depressants and other

adulterants in the available supplies made a clinical trial seem too dangerous. No one knew the exact botanical source of curare or the chemical composition of its active principle. In 1938 Richard C. Gill,(2) an American who had lived for years in the upper Amazonian jungles of Ecuador and who was familiar with the Indian folklore and mysticism which has surrounded the "flying death," as curare is called in the jungle, brought back to the United States the first adequate supply of the drug with properly labelled specimens of the various plants which are used by the Indians in the manufacture of crude curare. Professor A.R. McIntyre(3) of the University of Nebraska then subjected this supply of curare to the first adequate study by modern pharmacological methods. Through co-operation with the Research Laboratories of E.R. Squibb and Sons he was able to produce a purified product which exhibited the true curare action without toxic side effects and which he felt was safe for human experimentation. The present commercial product, which is known as Intocostrin (Extract of Purified Curare, Squibb), is marketed in 5 cc. vials of a pale amber liquid which contains 20 mg. of active curare substance to each cc. It is obtained from the single plant Chondrodendron tomentosum and has a selective action affecting first the muscles of the throat and neck, then skeletal muscles of the extremities, chest and abdomen, and the diaphragm last or not at all. It has no effect on involuntary or cardiac muscle in therapeutic doses.

The first large scale test of the new curare on human subjects was made by Professor A.E. Bennett(4) of the University of Nebraska who used it to soften the traumatic effects of convulsive shock therapy in psychiatric patients. This use for curare in conjunction with both metrazol and electric shock therapy has become widespread in mental hospitals, and now many thousand injections have been given without harmful effect. With this pharmacological and clinical evidence of the safety of Intocostrin we felt that it might be tried on patients under general

anaesthesia, and so at the suggestion of Dr. L.R. Wright we began using it in the operating room of the Homoeopathic Hospital of Montreal in January, 1942. We were immediately pleased with the results obtained and the absence of any harmful effect either during or after operation. Dr. Enid Johnson and I published a preliminary report[5] of our first 25 cases and we continued to use the drug cautiously in selected cases, becoming increasingly confident that we had hit upon something to make the anaesthetist's dream regarding relaxation come true.[6] Up to the present we have used curare in only 175 cases, because our preference has been to use it only when extra relaxation was required. Dr. S.C. Cullen[7,8] of the University of Iowa, who also began to use it in anaesthesia in 1942, has provided us with an impressive demonstration of the safety of curare in a much larger series of cases, since he began to give it routinely in every abdominal operation, and has now reported over 1000 administrations. Reports from other anaesthetists tell of equal success without any harmful effect. The evidence thus accumulated has led me to the conclusion that curare can be used with impunity in any case where muscular relaxation is required, provided facilities are always available for controlling respiration during the period of its action.

Curare acts on the neuro-muscular synapse probably by neutralization of the acetylcholine reaction. It effectively blocks synaptic transmission between preganglionic and postganglionic fibres of the sympathetic division of the autonomic nervous system. Its action does not extend to structures innervated by postganglionic fibres, such as glands and smooth muscle. There does seem to be, however, a contraction of the bowel itself, probably because of complete relaxation of the abdominal wall and quiet respiration. Curare is eliminated very rapidly, partly by destruction in the liver and partly by excretion unchanged by the kidneys. No evidence of any visceral damage has been produced and no direct effect on the heart reported. It may apparently be given to patients with damaged liver or kidney without any prolongation or intensification of the effect. We have used it

on some very poor risk patients quite harmlessly, although the cases where it is most needed for relaxation are healthy muscular individuals. Respiratory depression may occur following curare injection, and has been noted in about 10 per cent of our cases. However, this is always transitory and may easily be controlled by the same methods which we employ to control respiratory depression occurring from other causes during anaesthesia. An overdose causing complete respiratory paralysis can be overcome by artificial ventilation of the lungs with oxygen during the ten or fifteen minutes of paresis. Prostigmin bears a close resemblance to a true physiological antidote to curare since it acts to inhibit choline esterase and restore the acetylcholine preponderance at the myoneural junction. For this reason an ampoule of prostigmin should always be available when curare is used, although in our experience it has never been necessary to use it.

Apparently curare produces no analgesia, although the investigation of its action in this regard when given in full doses remains to be determined. I gave 5 cc. of Intocostrin (100 mg. curare) to one patient who was conscious, in order to demonstrate the effect on chronic muscular spasticity. He became almost completely paralyzed, particularly in the muscles of tongue and throat, and he had a terrifying sensation of impending death, although there was no respiratory depression or anoxia. So far as I could tell there was no analgesia. In twenty minutes he was completely restored to normal, spasticity and all, but he did not come back for another treatment. Because of the unpleasant subjective sensation of paralysis I do not recommend curare for use in full doses to conscious patients or to patients in whom spinal anaesthesia is wearing off unless they are very well sedated or a supplementary general anaesthetic is given. We have found, however, in agreement with Cullen and others, that curare may be very useful to facilitate bronchoscopy in a resistant muscular patient even when he is not asleep. In this situation the patient is probably so much concerned with the unpleasantness of the insertion of the

bronchoscope that he doesn't notice the muscular paralysis.

In our experience curare has proved most useful in securing complete abdominal muscular relaxation in patients under general anaesthesia, usually cyclopropane. We give it intravenously at any time during the operation when we see that extra relaxation would be advantageous. Cullen advocates its routine use in abdominal surgery, making the injection at about the same time as the skin incision, and repeating it if necessary during the operation. I have come to have so much confidence in the safety of curare that I have no objection to this technique, but in our experience relaxation continues to be satisfactory with cyclopropane alone in the majority of our cases. Now we use curare rather than push the cyclopropane, but even under these circumstances we are using curare in less than one fifth of our abdominal operations. The following table presents an analysis of the use of curare in 1000 consecutive operations at our hospital:

Total operations	- 1000	Curare used	- 86	or 8.6%	
Abdominal operations	- 478	" "	- 79	or 16.5%	
Appendectomies	- 228	" "	- 23	or 10.1%	
Hysterectomies	- 67	" "	- 22	or 32.8%	
Gall bladder and stomach	- 42	" "	- 19	or 45.2%	
Other abdominal	- 141	" "	- 15	or 10.6%	
		Bowel resection	- 4		
		Explor. laparotomy	- 2		
		Colostomy	- 2		
		Herniotomy	- 3		
		Salpingectomy, etc.	- 4		
Extra - abdominal operations	- 522	Curare used	- 7	or 1.3%	
		Haemorrhoidectomy	- 1		
		Tonsillectomy	- 1		
		Thyroidectomy	- 1		
		Bronchoscopy	- 2		
		Oesophagoscopy	- 1		
		Manipulation of foot	- 1		

It is noted that curare is, as might be expected, more often needed for upper abdominal and for pelvic surgery than for ordinary appendectomies, and in the extra-abdominal cases it has been usually to facilitate endotracheal intubation.

In all our cases curare has been given intravenously. The effect is produced within a few seconds, reaches its peak in two or three minutes and gradually wears off in fifteen or twenty minutes. When the patient is under general anaesthesia it is usually hard to say just exactly how much of the relaxation is due to the curare and how much to the anaesthetic agent and we have ordinarily been able to maintain satisfactory relaxation with cyclopropane throughout the whole operation following one injection of curare. However, if more relaxation is needed there is no objection to repeating the dose - I have done so a few times, and Cullen has given a second dose many times without any bad effect. Curare may be injected intramuscularly, but I have not used it this way in anaesthesia since it has seemed to me that the effect would be less certain and more difficult to control. Intocostrin is not irritating to subcutaneous tissues and I have seen no phlebitis or other reaction following any of our injections.

To the average adult patient I usually give a dose of 5 cc. of Intocostrin (100 mg. curare) in one intravenous injection. This has proved to be adequate in almost every case, and has had no harmful effect in any case except occasional respiratory depression, which, as I have said, is easily controlled. It is a simpler method than to give fractional doses according to the patient's requirement, as recommended by Cullen. Too small a dose will lead to disappointing results, as was the case with some of the earlier investigators - it is the old story of sending a boy on a man's errand. The doses being used in psychiatry for the minimizing of convulsion trauma are smaller than we recommend in anaesthesia, but I believe that in the operating room with facilities always at hand for the control of respiration the conditions are safer for large dosage than in most mental hospitals. Our patients have varied in age from 12 to 75 years, and the dose should be reduced in proportion to the weight of a child or to factors of frailness and asthenia in the aged. I believe that curare may safely be used with babies and quite small children, but I have had no experience along those lines and I

await with interest the reports of other workers.

As I have said, almost all our patients have been under cyclopropane anaesthesia with no added ether or other anaesthetic agent. There is no doubt that curare works ideally in combination with cyclopropane. I think, however, that it may be used safely with other agents, particularly with nitrous oxide and ethylene. Cullen has shown that with ether the dose of curare should be reduced to one third of that usually used during cyclopropane anaesthesia. Experimental studies have shown that this is because ether itself has a marked curariform action, and that the myo-neural junction is already partially paralyzed. If this factor is kept in mind curare may be used satisfactorily during ether anaesthesia, and relaxation and a quiet abdomen obtained without deep anaesthesia.

I have used curare in conjunction with sodium pentothal in only one case, but Dr. Fernando Hudon (9) of Quebec, who uses pentothal for much abdominal surgery, has obtained excellent results with the combination of Intocostrin and pentothal in a fairly large series of cases. There seems to be no significant change in respiration and pulmonary ventilation with this combination.

Pre-operative medication does not seem to have any effect on curare action. Cullen has stated that atropine or scopolamine is apparently essential in the premedication. Our experience has not borne out this theory, as at least half of our patients have received neither of these drugs, and I can see no difference in the curare action. Nor have we had any special difficulty with hypersecretion of mucus which might be attributed to curare. About 10 per cent of our curare patients received a moderate dose of avertin previous to cyclopropane, and here again there has been no significant change in the curare effect. The complete absence of all postoperative effects from curare has been one of the most striking and encouraging features of this whole investigation. This has been true in my own experience and is recorded by everyone else whose reports I have heard.

What may the future hold as to the place of curare in anaesthesia ? A much longer and wider clinical and laboratory investigation must take place before this point can be finally settled. However, in view of our experience so far I venture to predict that curare will have the effect of:

Firstly - reducing the demand for spinal anaesthesia with its attendant hazards and complications, since the reason for many spinal anaesthetics is that adequate abdominal relaxation may be obtained; and

Secondly - increasing the incidence of pure cyclopropane or pentothal anaesthesia, without the addition of ether, for abdominal surgery and thus reducing postoperative complications.

Surgeons who have been able to overcome their detective story dread of curare, "the arrow poison," and have allowed us to use it on their patients, are unanimously enthusiastic about the results obtained. I would like to add a word of thanks to those long-suffering surgeons of my own hospital who have put up for many years with my tinkering in anaesthesia. Without their co-operation none of what I may have accomplished would have been possible. I am glad that at last I have been able to give them something which not only keeps their patients alive but keeps their own blood pressures down and makes their work easier. One word more of caution - the anaesthetist is still more important than the agent used, and curare is not a plaything for the inexperienced.