DIMETHYL ETHER OF D-TUBOCURARINE IODIDE AS A CURARIZING AGENT IN ANAESTHESIA FOR THORACIC SURGERY

BY

HOWARD BRUCE WILSON, M.B., Ch.B., D.P.H.
D.A., F.F.A.R.C.S.

Senior Anaesthetist

HELEN E. GORDON, M.B., Ch.B., D.A.
Anaesthetist

AND

ALFRED W. RAFFAN, M.B., Ch.B., D.A.
Anaesthetist

*Royal Aberdeen Hospital for Sick Children and Thoracic Unit,
Aberdeen*

Until comparatively recently the favourite agent for producing anaesthesia for thoracic operations has probably been cyclopropane. The use of this gas, combined with controlled respiration and carbon dioxide absorption, reduces the movements of the diaphragm to a minimum and so gives a tranquil field of operation. On the other hand, the highly explosive nature of cyclopropane greatly restricts or entirely prevents the use of any form of diathermy during its administration. This is a real handicap to the surgeon and tends appreciably to prolong operations. Another disadvantage is the possible occurrence of the so-called cyclopropane shock in the immediate post-operative stages.

With the introduction of curare and other similar agents a still better anaesthetic technique has become available for these operations. With this new method, general anaesthesia is obtained by the use of soluble thiopentone in combination with nitrous oxide and oxygen in closed circuit with a soda-lime canister for carbon dioxide absorption. The necessary diaphragmatic paralysis is obtained by intermittent doses of D-tubocurarine chloride, and diathermy can be freely used at all stages of the operation without danger of explosion.

Careful case records taken in a busy thoracic unit showed that, while this D-tubocurarine technique represented a great advance on previous methods, it had some disadvantages. These, though not unduly restricting its use, suggested that some other curarizing agent might be discovered which would approach the ideal more nearly still.

Some months ago one of us (H. B. W.) was given the opportunity, through the Joint Anaesthetics Committee of the Medical Research Council and the Royal Society of Medicine, to carry out a clinical investigation of a new product, the dimethyl ether of D-tubocurarine iodide, with a view to determining whether it had advantages over D-tubocurarine chloride, particularly in two respects: Did it release or facilitate the release of histamine to a less extent? and, Did it have less effect in paralysing autonomic ganglia?

Pharmacology

The dimethyl ether of D-tubocurarine iodide is obtained by treating D-tubocurarine chloride with two molecular equivalents of sodium hydroxide and then with two molecular equivalents of methyl iodide, all in methanol solution (Collier, Paris, and Woolf, 1948); the two free hydroxyl groups are thus methylated, and the salt is changed from

the chloride to the iodide. These differences are shown in the following structural formulae.

Much animal experimentation has been carried out with this drug, both in this country by Collier, Paris, and Woolf (1948), and in the U.S.A. by Swanson, Henderson, and Chen (1949) and others; this work is reviewed in the article by Collier and Hall at p. 1293 of this issue. As might be expected from its chemical structure, the pharmacology of the new preparation is generally similar to that of D-tubocurarine chloride; but in the rabbit and cat it has been found to be seven to ten times more potent, and in some species its action is more rapid and prolonged. There is evidence, too (Collier and Paton, personal communication), that it is no more active in releasing histamine and in paralysing autonomic ganglia. In man the drug has been used as an adjunct to anaesthesia in 100 cases reported by Stoelting, Graf, and Vieira (1948).

With this evidence before us it seemed justifiable to try it in the thoracic unit, and to employ it for a period as the curarizing agent in major chest operations in place of D-tubocurarine chloride.

On examination of our previous records, when D-tubocurarine chloride had been used we had observed that after a period of two and a half to three hours there was a fairly constant depression of the systolic blood pressure accompanying a rise in the diastolic pressure—and this in spite of blood replacement. We had concluded that it might be due to histamine release from devitalized tissues facilitated by the presence of D-tubocurarine chloride in the circulation. Acting on this assumption, we began an investigation into the value of antihistamine drugs given in combination with D-tubocurarine chloride, with the object of counteracting the effects of histamine release. This will be the subject of a further paper at a later date.

The Investigation

The anaesthetic technique employed in our investigation into the value of the dimethyl ether of D-tubocurarine chloride was identical with our previous practice. It consisted of premedication with "omnupon" and scopolamine in orthodox dosage, induction of anaesthesia with soluble thiopentone, injection of dimethyl ether of D-tubocurarine iodide, and intubation under direct vision with as large a cuffed endotracheal tube as could be conveniently used. A 50:50 mixture of nitrous oxide and oxygen was then administered in a closed circuit with an intentional slight leak. Light-plane anaesthesia was maintained by fractional doses of soluble thiopentone introduced into the blood-transfusion tubing, and a quiet diaphragm achieved by

giving repeated doses of dimethyl ether of D-tubocurarine iodide by the same route.

We have based the dosage of the dimethyl ether of D-tubocurarine iodide on body weight; it has initially been of the order of 1 mg. per stone (6.35 kg.). We feel that it is safer to dose a patient adequately than to underdose him with any curarizing agent, to lessen the tendency to bronchospasm. Incremental doses of the dimethyl ether of D-tubocurarine iodide are of the order of 3 mg., and their administration is guided by the degree of diaphragmatic activity.

We were impressed by one striking improvement in our results on changing to the new compound—namely, the extreme ease with which a lung or lobe which had been allowed to collapse could be reinflated. Using D-tubocurarine chloride we had always been able to reinflate a lung or lobe, but quite firm pressure on the bag was often required, more particularly in the later stages of the operation. Using dimethyl ether of D-tubocurarine iodide, however, we found that the pressure required to reinflate the lung was much less and remained so throughout the operation. What is the explanation? Is it that when using D-tubocurarine chloride an excess of circulating histamine, with its tendency to increase bronchial muscle tone, is released as the operation proceeds and trauma increases, and that with the use of dimethyl ether of D-tubocurarine iodide there is less histamine release and consequently less stimulation of the tone of the bronchial tree?

There was also a definite change in the blood pressure picture. The fall in systolic blood pressure with an accompanying rise in diastolic pressure previously noticed did not seem to occur to the same extent, or, if it did, was manifest only at a much later stage than with D-tubocurarine chloride.

Conclusions

Owing to the absence, through illness, of one of us (H. B. W.), this communication is not as complete as we would desire and should be regarded as an interim report. With that limitation, our conclusions from using the dimethyl ether of D-tubocurarine iodide as the curarizing agent in 100 cases of major intrathoracic procedures, including pneumonectomies, lobectomies, and mediastinal tumours, are as follows:

1. Dimethyl ether of D-tubocurarine iodide seems to be 2 to 2½ times more potent than D-tubocurarine chloride.
2. The duration of action on diaphragmatic activity is a little shorter than with D-tubocurarine chloride and subsequent doses are required at intervals of 20 to 25 minutes.
3. Clinically there seems to be less release of histamine, as is evidenced by (a) maintenance of systolic and diastolic blood pressures, and (b) ease of inflation of collapsed lung tissues, particularly at the later stages of the operation.
4. In all other ways, as would be expected, the two preparations seem similar in action.

Recent work by Pelikan, Sadove, and Unna (1950) on the relative potency of D-tubocurarine chloride and the curare-like drugs gives support to our clinical findings on the relative strengths of D-tubocurarine chloride and the dimethyl ether of D-tubocurarine iodide, as it does to the relative duration of action of these preparations.

Our impressions are that in the dimethyl ether of D-tubocurarine iodide we have a curarizing agent which has all the advantages of D-tubocurarine chloride and which, from our small series of cases, seems to have less tendency towards histamine release. In no case had we any cause for anxiety, either on the table or post-operatively,

which could be referred to the use of dimethyl ether of D-tubocurarine iodide. However, as of passing interest, it may be noted that in one recent thoracotomy, using D-tubocurarine chloride, a frank bronchospasm occurred and was confirmed by bronchoscopy. Fortunately it responded to appropriate measures.

No evidence of delayed detoxication of the dimethyl ether of D-tubocurarine iodide has been noted, nor have we seen any undue reactions to the drug. The possibility of idiosyncrasy to iodides should, however, be borne in mind when administering it.

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NINE BLOOD-GROUP ANTIBODIES IN A SINGLE SERUM AFTER MULTIPLE TRANSFUSIONS

BY

J. O. COLLINS, M.D.

RUTH SANGER, B.Sc., Ph.D.

F. H. ALLEN, Jun., M.D.

AND

R. R. RACE, Ph.D., M.R.C.S.

(From the Clinical Laboratory, Waterbury Hospital, Waterbury, Connecticut; the Blood Grouping Laboratory, Children's Medical Center, Boston; and the Medical Research Council Blood Group Research Unit, Lister Institute, London)

The complete case record upon which this paper is based presents many facets that might be explored with interest by specialists in various fields of medicine and biology. One of the most striking features concerns the large number of antibodies this splenectomized patient was able to produce in response to a comparatively small number of transfusions administered at irregular intervals over a period of several years. Briefly the history is as follows.

Case History

Mrs. F. W., a 40-year-old white housewife, was first admitted to the Waterbury Hospital in September, 1933, for delivery. This was her second pregnancy, the first having terminated with toxæmia and premature stillbirth. After normal delivery of a normal child it was discovered that she had a large spleen. This she stated had been present for 12 years. She was re-admitted for splenectomy in March, 1937. Blood studies on three occasions before splenectomy showed no anaemia or other evidence of blood dyscrasia. The spleen weighed 1,100 g., and increased fibrous tissue with many scattered islands of myelopoiesis and erythropoiesis were seen microscopically. Also many megakaryocytes were noted. Splenectomy was followed by mild anaemia, for which two blood transfusions were given without reaction.

During the next 12 years the patient was repeatedly admitted for anaemia and received several transfusions, as indicated in