UNDESIRABLE SIDE-EFFECTS FROM DECAMETHONIUM IODIDE

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Decamethonium iodide (C10) is a cheap and easily prepared compound. The short duration of muscular relaxation which it produces and the apparent absence of undesirable side-effects (Hewer *et al.*, 1949; Organe, 1949; Davies and Lewis, 1949; Bailey and Murphy, 1951) led us to suppose that this drug could be employed usefully in surgical procedures requiring relaxation for short periods. It was also used in repeated doses to produce relaxation for longer periods.

Present Investigation

In a series of 233 administrations of C10 to subjects between the ages of 16 and 75 (see Table) we have noted one case of cumulative action similar to those reported by Gray (1950) and Barry *et al.* (1951). We also had four cases which exhibited cardiovascular abnormalities.

Analysis of 233 Administrations of C10

Operation	No. of Cases
Appendectomy	67
Hysterectomy and gynaecological operations	25
Herniorrhaphy	49
Urogenital operations	26
Haemorrhoidectomy	23
For perforated peptic ulcer	8
Exploratory laparotomy	5
Operations on the stomach	7
Operations on the bowel	8
Oesophagoscopy	4
For laryngeal spasm	11

The antidote to C10 is pentamethonium iodide (C5). A fall in blood pressure follows the intravenous injection of the antidote. It is stated that this reaction is likely to be severe in hypertensive or anaesthetized subjects (Enderby, 1950; Davison, 1950). This has been held to be one of the disadvantages of C10 compared with D-tubocurarine and gallamine triethiodide, the antidote to the latter drugs being neostigmine. It has now been suggested that the use of neostigmine in certain cases is not without danger. Neostigmine is given with atropine intravenously, the atropine to prevent excessive bronchial secretion which may be produced by the neostigmine. Deaths have been reported following the simultaneous intravenous injection of atropine and neostigmine (Macintosh, 1949; Clutton-Brock, 1949). Electrocardiographic recordings taken during anaesthesia have shown that ventricular arrhythmias and ventricular tachycardia have occurred after the intravenous injection of atropine in subjects who have increased carbon dioxide tension (Johnstone, 1951). A subject may be in this condition if he has not recovered from the intercostal paralysis produced by a relaxant drug. Johnstone also states that the intravenous injection of neostigmine may in some cases cause ventricular tachycardia. He suggests that these factors may have caused death in the cases reported by Macintosh and Clutton-Brock. We believe that in our present state of knowledge the antidote should not influence the choice of relaxant drug. Assisted respiration should be maintained, with an endotracheal tube *in situ*, until respiratory excursions are adequate, if there is any residual intercostal paralysis after the administration of a relaxant drug.

"Syncurine" brand of C10 was used: a test dose was not given. Paton and Zaimis (1950) state that circulating

adrenaline antagonizes the action of C10, and that misleading results will be obtained by administering this drug to unanaesthetized and apprehensive subjects. Anaesthesia was induced with thiopentone in all cases. An initial dose of 3 mg. of C10 was given, either immediately after induction to facilitate intubation or about five minutes before relaxation was required by the surgeon. Anaesthesia was maintained with cyclopropane and oxygen; minimal ether and oxygen; gas, oxygen, and "trilene"; or intermittent thiopentone, gas, and oxygen. It was sometimes necessary to give a further 2 or 3 mg. of C10 if relaxation produced by the initial dose was inadequate. We found that subjects of the same build and having similar muscular development varied in their response to the initial dose. Some showed no obvious alteration in respiratory excursions and inadequate relaxation. Others exhibited varying degrees of intercostal paralysis which lasted from five to fifteen minutes. The return of muscle tone was rapid and unpredictable, a source of embarrassment to the surgeon and anaesthetist.

Recent work on the mode of action of relaxants (Paton and Zaimis, 1950) explains why it is not easy to compare the effects of C10 and D-tubocurarine. The former drug has a similar action to that of acetylcholine, the muscle end-plate is depolarized and a neuromuscular block produced (Burns and Paton, 1950). D-tubocurarine is said to raise the threshold of the motor end-plate to acetylcholine. Factors present during anaesthesia differ in their effects on the relaxation produced by the two relaxant drugs. For example, ether slightly antagonizes C10, but a synergistic effect is seen with D-tubocurarine with a resulting increase in paralysis produced. The presence of circulating adrenaline increases the stimulant effect of C10 and decreases the maximum paralysis. The opposite effect occurs with D-tubocurarine.

We found that C10 facilitated oral intubation and relaxed a laryngeal spasm enough to permit the passage of an endotracheal tube. It was also used in subjects who were heavy cigarette smokers. After induction with thiopentone, the coughing and spasm encountered during the transition from thiopentone to ether or trilene could be avoided.

Case 1

A small man aged 65 with chronic bronchitis and occasional extrasystoles was operated on for rectal prolapse. His blood pressure was 160/80. Premedication with morphine, 1/6 gr. (11 mg.), and atropine, 1/100 gr. (0.65 mg.), was given 45 minutes before operation. Anaesthesia was induced with 0.2 g. of thiopentone and maintained with cyclopropane, oxygen, and minimal ether. Enough relaxation of short duration for oral intubation to be performed was produced by 3 mg. of C10 injected intravenously. Two further doses of 2 and 3 mg. were given, the final one 30 minutes after induction of anaesthesia. Intercostal paralysis was produced but not apnoea. The operation was completed 45 minutes after the final dose of C10 was given. The respiration was shallow and diaphragmatic only, and there was marked tracheal tug. Cyanosis could be avoided only by rhythmic inflation of the lungs with oxygen. One hour later respiratory excursions were greater and there was no cyanosis when breathing air unassisted. Some intercostal paralysis and tracheal tug still persisted. The patient was now semi-conscious and his general condition was satisfactory. He was returned to the ward with the endotracheal tube *in situ* and oxygen was administered through a B.L.B. mask; 45 minutes later he coughed out the tube. He was now fully conscious, the respiratory excursions had returned to normal, and there was no residual paralysis. Post-operatively there was some exacerbation of his bronchitis. The sputum was expectorated easily and improvement rapidly occurred.

Case 2

A man aged 53, in good general condition, was operated on for repair of a ventral hernia. Premedication was with "omnopon," $\frac{1}{2}$ gr. (22 mg.), and hyoscine, 1/150 gr.

(0.43 mg.), given two hours before operation. The nasal cavities were sprayed with 10% cocaine, and anaesthesia was induced with 0.4 g. of thiopentone, nitrous oxide, oxygen, and trilene. Blind nasal intubation was performed and maintenance continued with nitrous oxide and oxygen. A further 0.2 g. of thiopentone was given in fractional doses, some respiratory depression was produced, and respiration was assisted. Respiratory excursions were adequate when the first incision was made. When 3 mg. of C10 was injected intravenously there was an immediate onset of paroxysmal tachycardia, the pulse being uncountable and grossly irregular. The tachycardia lasted a few seconds only, the arrhythmia about two minutes. During this time there was a fall in blood pressure. The pulse rate then fell to 58 and returned to normal in a few minutes. As the 3 mg. of C10 did not produce adequate relaxation on vinesthene-ether mixture was added. An electrocardiogram taken half an hour after the onset of the cardiovascular disturbance showed no abnormality. The general condition, blood pressure, and pulse rate remained satisfactory during the rest of the operation, and the post-operative progress was uneventful.

Case 3

An obese woman aged 53, in good general health, had a subtotal hysterectomy for uterine fibroids. Her blood pressure was 140/80. Premedication with morphine 1/6 gr. (11 mg.), and atropine 1/100 gr. (0.65 mg.), was given 45 minutes before operation. Anaesthesia was induced with 0.4 g. of thiopentone and maintained with cyclopropane and minimal ether. An orotracheal tube, lubricated with 10% cinchocaine hydrochloride ointment, was passed under direct vision. A pharyngeal pack was inserted to prevent gases being blown into the oesophagus should assisted respiration become necessary. The cyclopropane was turned off and anaesthesia maintained with oxygen and minimal ether. The blood pressure was now 120/80 and the pulse rate 80. The patient was placed in the Trendelenburg position and 3 mg. of C10 injected intravenously. Immediately after the injection the pulse rate dropped to 60 and she became pale. Ten minutes later the pulse rate was still 60 and the blood pressure 90/30. There were diminished respiratory excursions and relaxation was adequate. Respiration was assisted and there was no cyanosis. "Methedrine," 15 mg., was injected slowly intravenously and the same dose intramuscularly. In 10 minutes the blood pressure rose to 100/60 and the pulse rate to 70. Thirty minutes later the blood pressure was 120/70 and the pulse rate 90. Respiratory excursions were adequate and there was no tracheal tug. At the end of the operation there was no residual paralysis and the post-operative progress was satisfactory except for some vomiting on the first day.

Case 4

A thin man aged 48, in good general condition, was operated on for the removal of a ureteric calculus. His blood pressure was 130/80. Premedication with hyoscine, 1/150 gr. (0.43 g.), and potassium bromide and chloral, 30 gr. (2 g.) of each, was given two hours before operation. Anaesthesia was induced with 0.5 g. of thiopentone and continued as in Case 3. The patient was placed in the lateral position; the blood pressure was now 120/70 and the pulse rate 80, and 3 mg. of C10 was injected intravenously. Relaxation was inadequate and ten minutes later a further 2 mg. was injected. The pulse rate fell at once to 50 and the blood pressure to 90 systolic. There was marked intercostal paralysis and tracheal tug; respiration was assisted. As methedrine had improved Case 3, it was injected as before. In 20 minutes the blood pressure rose to 140/80 and the pulse rate to 80. The respiratory excursions were now adequate. The operation was completed in 50 minutes and recovery from the anaesthetic was uneventful.

Case 5

This case of an obese woman aged 53 is included, though other factors present were capable of producing the cardio-

vascular irregularities. Her blood pressure was 210/100. The pulse rate was 80 and regular and there was no history of anginal attacks. The operation performed was a subtotal hysterectomy and the removal of a large ovarian cyst. Premedication with hyoscine, 1/150 gr. (0.43 g.), and potassium bromide and chloral, 20 gr. (1.3 g.) of each, was given two hours before operation. Anaesthesia was induced with 0.5 g. of thiopentone and continued as in Cases 3 and 4. The blood pressure was now 180/90 and the pulse rate 90 and regular in rhythm. The patient was placed in the Trendelenburg position and 3 mg. of C10 was injected intravenously. Fair muscular relaxation was obtained, the respiratory excursions were diminished, and respiration was assisted. Twenty minutes later the surgeon had great difficulty in delivering the cyst from the wound and more relaxation was asked for: 2 mg. of C10 was injected intravenously and at the same time the cyst was ruptured while attempts were being made to deliver it. The blood pressure fell to 100/40 and the pulse rate to 40. Respiration was assisted and 15 mg. of methedrine was injected slowly intravenously. A further 15 mg. was injected intramuscularly. In 30 minutes the blood pressure had risen to 200/100 and the pulse rate to 90. At the end of the operation the respiratory excursions were adequate and the general condition was satisfactory.

Comment

Some justifiable criticisms can be made of the dosage of C10 employed. In Case 1 a relatively large dose, 7 mg. in all, was given to a frail and elderly man with chronic bronchitis. Case 5 having received 3 mg. of C10, further relaxation should have been obtained by deepening anaesthesia. It is now our opinion that it is advisable to withhold relaxant drugs from elderly and obese subjects who are to be placed in the lateral or Trendelenburg positions. In the lateral position there is a 10 to 12% loss in vital capacity (Case and Stiles, 1946). With the Trendelenburg position the loss is 14 to 20% with 20 to 22.5 degrees of tilt (Altschule, 1943; Case and Stiles, 1946). In this position the bowels and omentum fall on the diaphragm or are pressed there by abdominal packs. The alterations in pulse rate and blood pressure occurred in subjects over 45 years of age, in all of whom an endotracheal tube had been passed.

In Case 5 the changes coincided with the rupture of an ovarian cyst and therefore a sudden decrease in intra-abdominal pressure in a hypertensive subject. These abnormalities all occurred at the moment of injection of C10. They could, however, be the result of irritation of the larynx and trachea in a light plane of anaesthesia by the endotracheal tube causing reflex vagal inhibition. It is also possible that the inhalation of too great a concentration of anaesthetic vapour, made easy by the presence of an endotracheal tube, may stimulate a pulmo-cardiac reflex. We have not encountered such abnormalities when using D-tubocurarine or gallamine triethiodide in similar circumstances.

Summary

Decamethonium iodide was administered to 233 subjects between the ages of 16 and 75.

The degree of muscular relaxation and respiratory paralysis was found to be variable when using a standard dose of 3 mg.

One case of cumulative effect and four showing cardiovascular abnormalities were encountered.

ADDENDUM.—Since writing this article we give atropine and neostigmine if there is some residual paralysis following the use of D-tubocurarine and gallamine triethiodide, but the drugs are not given simultaneously. The atropine is injected intravenously ten minutes before it is proposed to inject the neostigmine. If the pulse rate is slow and there is no rise in rate after the injection of atropine, neostigmine is not given.

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“NILODIN” IN TREATMENT OF SCHISTOSOMA HAEMATOBIIUM

BY

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Owing to reports by various workers that “nilodin” brand 1-diethylaminoethylamino-4-methylthioxanthone hydrochloride, sometimes referred to in the literature as “miracil D,” has a definite place in the treatment of bilharziasis (Blair *et al.*, 1947; Abdel Azim *et al.*, 1948), the following observations on seven cases of urinary *S. haematobium* treated with the drug may be useful. The number of cases is so small that no claim is made that the results are significant.

Case Reports

Case 1.—A Sudanese girl aged 12 was given 15 mg. of nilodin per kg. of body weight daily for five consecutive days. Her urine was examined daily and showed a large number of *S. haematobium* ova, red blood cells, and pus cells. Her initial weight was 35 kg., but she had lost about 6 kg. by the end of the five days' treatment. Her skin, sclerotics, mucous membranes, and urine were a deep yellow. Although her appetite was impaired she was not troubled by nausea or vomiting and she tolerated the drug fairly well. Ten days after the cessation of treatment the urine was still yellow, and, although the red cells and pus cells were fewer than before treatment, there were still viable ova. During an interval of a month without treatment viable ova were constantly present in the urine, but she regained her initial weight and lost the yellow coloration. A second course of 15 mg. per kg. of body weight daily for five days was given, and almost the same effects were encountered as during the first course. After another month's interval a third course was given. The urine still contained viable ova one month after the third course—that is, 105 days from the beginning of treatment.

Case 2.—A Sudanese man aged 23 was given 15 mg. of nilodin per kg. of body weight daily. He took the drug for two days and then developed a severe gastritis, which showed itself in the form of nausea and troublesome and continuous vomiting, together with a slight rise in temperature. He lost weight rapidly and looked toxic; the skin, sclerotics, and urine were yellow. After a lapse of about four months he was persuaded to undergo another course of treatment. This time, to soothe the mucous membrane of the stomach, he was put on a bismuth mixture two days before the beginning of treatment and also during treatment. He took the tablets for two days, but on the third day severe vomiting developed and he could not continue with the treatment. The urine contained a large number of viable ova two months after this attempt.

Case 3.—A Sudanese boy, aged 13 and weighing 40 kg., was given 15 mg. of nilodin per kg. of body weight for two days. He then developed severe and troublesome vomiting.

Treatment was stopped on account of intolerance. His urine contained a large number of viable ova at the end of this treatment.

Case 4.—A Sudanese man aged 45 was given 15 mg. of nilodin per kg. of body weight (weight, 60 kg.). He took the drug for two days; it was then stopped on account of intolerance, as shown by severe and troublesome vomiting.

Case 5.—A Sudanese woman aged 53 was infected with *S. haematobium*. Her liver and spleen were not palpable. There were no urinary complications. Examination of the urine revealed red blood cells, pus cells, and a large number of ova. She was put on 15 mg. of nilodin per kg. of body weight (weight, 50 kg.). The tablets were spread over the day and given after meals. On the third day of treatment she lost her appetite and developed a yellow discoloration of the skin and conjunctivae. However, she continued treatment for five days, her urine still containing ova of *S. haematobium*. After a fortnight's rest a second course of 700 mg. of nilodin daily for five days was given. Sickness and yellow discoloration of the skin again ensued. Her urine still contained viable ova. A third course of 700 mg. daily for five days was given a fortnight later. This time she developed severe vomiting and profuse sweating, and lost 7 kg. in weight. Viable ova were still present in the urine 75 days from the beginning of treatment.

Case 6.—A Sudanese boy aged 15 who suffered from urinary *S. haematobium* was given 15 mg. of nilodin per kg. of body weight daily. On the third day he developed severe vomiting and yellow discoloration of the skin, conjunctivae, urine, and mucous membranes, and refused to continue treatment. He lost 3 kg. in weight. His urine still showed a large number of viable ova.

Case 7.—A Sudanese man aged 26 with urinary *S. haematobium* was given 15 mg. of nilodin per kg. of body weight. He contracted his disease five years before and had had two courses of antimony treatment without being cured. On the third day he developed vomiting and yellow discoloration of the skin, but continued the treatment until the fifth day. He lost 4 kg. in weight. His urine contained viable ova a fortnight from the beginning of treatment. He declined to have a second course of nilodin.

Discussion

The treatment of schistosomiasis with antimony tartrate, which was started some 35 years ago by Christopherson (1918) in the Sudan, is not entirely satisfactory. The therapeutic dose of antimony is not far removed from the toxic dose, and the relapse rate in treated cases is high. Another disadvantage of the drug is that it is given by the intravenous route. For all these reasons a new drug which can be taken by mouth is welcome. When nilodin became available I took the opportunity of trying it on cases of urinary *S. haematobium*.

Only one of the seven cases treated tolerated the drug fairly well. The other six showed signs of toxicity, usually on the third day. Yellow discoloration of the skin and mucous membranes, loss of appetite, vomiting, and rapid wasting were the predominant signs. The use of bismuth preparations did not help in decreasing the toxicity of nilodin. In most of the cases the intolerance was so great that it was not possible to complete the treatment. No case was cured. The patient who tolerated the drug was given three courses of treatment, but she continued to pass viable ova 105 days after the beginning of treatment.

From so small a number of cases no conclusions can be drawn regarding the therapeutic value of nilodin. The intolerance to the drug among Sudanese is in my opinion a deterrent to its use for mass treatment.

Summary

Seven cases of *S. haematobium* were treated with nilodin.

None of the seven cases was cured as the result of treatment.