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“NILODIN” IN TREATMENT OF SCHISTOSOMA HAEMATOBIMUM

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.

The toxicity of the drug is a deterrent to its use in the mass treatment of *S. haematobium* in the Sudan.

I am indebted to Brigadier J. S. K. Boyd for the supplies of nilodin used in the cases here recorded; to Dr. R. Kirk for his help and encouragement; and to the Director, Medical Services, Ministry of Health, Sudan, for permission to publish these observations.

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SELF-EXPERIMENTS WITH SUCCINYL- CHOLINE CHLORIDE

A NEW ULTRA-SHORT-ACTING MUSCLE RELAXANT

BY

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The purpose of this paper is to describe the action, in man, of a new synthetic muscle relaxant. Our tests were carried out with the aim of proving the safety and specific action of succinylcholine chloride (S.C.C.) as a short-acting curarizing agent for patients under anaesthesia.

With the muscle relaxants in use in clinical anaesthesia a more superficial plane of general anaesthesia can be maintained, to the benefit of the patient. The introduction of curare (Griffith and Johnson, 1942) was followed by the development of synthetic relaxing agents, the best known of which to-day are "flaxedil" (gallamine triethyl iodide) (Bovet, Depierre, *et al.*, 1947, 1949; Mushin *et al.*, 1949) and decamethonium iodide or bromide ("eulissin," "syncurine," C10) (Paton and Zaimis, 1948, 1949; Organe, 1949; Vetten and Nicholson, 1950). The lack of sufficient controllability, the occasional prolonged curarization, and the more or less marked side-effects (release of histamine and blockade of the autonomic ganglia) are the main disadvantages of all the compounds mentioned, be their paralyzing effect due to a true blockade at the neuromuscular junction, as with D-tubocurarine and flaxedil, or due to depolarization of the end-plate and its surrounding, as is the case with decamethonium (Alam *et al.*, 1939; Comroe and Dripps, 1946; Vetten and Nicholson, 1950; Burns and Paton, 1951).

Succinylcholine iodide (S.C.I.) was first described by Bovet, Bovet-Nitti, *et al.* (1949). Its strong paralyzing power was recognized in animals, but no clinical tests were undertaken. Ginzel, Klupp, and Werner (1951a, 1951b, 1951c), at the Pharmacological Institute of Vienna University, examined thoroughly both S.C.I. and S.C.C.

The Properties of S.C.C.*

The chemical formula of S.C.C. is

*The makers, Oesterreichische Stickstoffwerke A.G., Linz, Austria, kindly furnished the necessary amounts of S.C.C. for these experiments and the clinical evaluation. The drug was named "M115" when in the experimental stage, and has now been registered under the name of "Iysthenon."

Physical Properties.—S.C.C. is supplied (as dihydrate) in 5-ml. ampoules containing 20 mg. of the substance in 1 ml. The solution is stable and has frequently been kept for several weeks outside the refrigerator without any decomposition becoming apparent. It is miscible with solutions of thiopentone and also with pethidine. No decrease of the usual effect could be observed when the drug was used in any of these mixtures.

Pharmacology.—S.C.C. was tested in frogs, cats, pigeons, and dogs in comparison with other compounds with a similar chemical structure (Ginzel *et al.*, 1951a, 1951b, 1951c). The entire series showed nicotine-like stimulating effects as well as muscular paralysis. S.C.C. had the strongest neuromuscular blocking effect and the weakest stimulating action to the autonomic ganglia. In artificially ventilated cats some slight rise in blood pressure did not occur until doses as high as several hundred times the paralyzing dose were being given. The paralyzing effect on the skeletal muscle is due to the same mechanism as with decamethonium: depolarization of the end-plate region (Ginzel *et al.*, 1952). Its action, therefore, is not counteracted by anti-choline-esterases as is the case with D-tubocurarine and flaxedil. It may even be prolonged and intensified to some extent. There appears to be the same antagonism between S.C.C. and curare as has previously been described for decamethonium and curare (Paton and Zaimis, 1949). Since S.C.C. is probably broken up by enzymatic hydrolysis into the non-effective monocholine ester of succinic acid and free choline within a matter of minutes, no antidote is felt to be needed in clinical practice.

Methods and Dosage

From previous tests with other synthetic curarizing agents (Mayrhofer and Hassfurth, 1951) the fact was known that sensibility to these compounds varies widely between different animals and humans.

For the self-experiments on an unanaesthetized 30-year-old male (O. K. M.) of 176 lb. (80 kg.) body weight only the intravenous route was used. In the first three experiments the injections were given fast (within two seconds). The doses varied between 0.125 and 0.375 mg./kg. In the next two tests the drug was injected slowly (within two minutes). The doses were 0.25 and 0.5 mg./kg. body weight. Finally, in an attempt to maintain a constant degree of relaxation and to regulate the depth of muscular paralysis at will, a continuous drip of a solution containing 2 mg. per ml. in normal saline was set up. No medication other than oxygen by facemask was given before, during, and after the experiments.

Three members of our medical staff assisted in the tests. One administered oxygen from an anaesthetic machine and conducted the necessary artificial respiration. The second injected the drug and took pulse and blood-pressure readings. The third took electrocardiographic readings and kept the records. Electrocardiographic tracings were taken before, during, and after the experiments, with the exception of the first two, in which only the blood pressure, pulse, and respiratory rate were recorded.

Results

Experiment 1.—May 11, 1951. 10 mg. S.C.C. (0.125 mg./kg.) injected within two seconds. Effect:—After 30 seconds: onset of muscle weakness, double vision, ptosis, muscle-twitching of eyelids, masseter, arms, legs, and glutei. After 60 seconds: partial paralysis of respiratory muscles; difficulties in speaking; head and arms cannot be raised. After 90 seconds: effect decreasing; good abdominal relaxation. After 120 seconds: arms can be lifted; head still very heavy; respiration still slightly depressed; tone of abdominal muscles returning; speech almost normal; jaw relaxed; eye muscles still weak. After 180 seconds: effect completely worn off. During this experiment no artificial or assisted respiration was necessary. Blood pressure and pulse showed no changes.