HAFFKININE (ACRIQUINE), AN ATEBRIN-LIKE COMPOUND PREPARED IN INDIA, IN INDIAN STRAINS OF MALARIA

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SINCE the discovery of the antimalarial properties of atebrin and its successful use in the routine treatment of malaria, efforts have been made in other countries to prepare acridine derivatives of a similar nature and with similar properties. In France, 'quinacrine', a compound with the same constitutional chemical formula, was prepared and successfully tested, while in the Union of Soviet Socialist Republics 'acriquine' a similar compound was synthesized. A comparative study of the actions of these two compounds on malarial infections reveals no difference. They destroy all the stages of the three species of malarial parasites with the exception of the gametocytes of *P. falciparum*. Like atebrin these compounds are mainly excreted through the kidneys and traces of them were found in the urine for a considerable period.

Recently, workers in the Haffkine Institute, Parel, Bombay, have prepared a similar acridine derivative the therapeutic efficacy of which has been tested by us on a series of eight cases in the Carmichael Hospital for Tropical Diseases. The compound was at first called 'Haffkinine' but this name has now been changed to 'acriquine' and in this paper we have given the summary of results of these trials.

After the patients were admitted into the hospital a thorough physical examination was carried out; the peripheral blood was examined and a rough estimate of the number of parasites, both sexual and asexual, was also made. Except in urgent cases, the patients were put on a simple alkaline mixture and the antimalarial treatment was not started until the parasitic counts were fairly constant for two or three consecutive days. The pulse rate, blood pressure and respiration were recorded. Daily counts of parasites in the peripheral blood during this period enabled us to watch the progress of the patients and gave us information with regard to the intensity of the infection and the action of the drug. If parasites in the peripheral blood were scanty, these were allowed to increase till the count was fairly advanced, and rigors and other symptoms were pronounced before the drug was administered. 'Haffkinine' (acriquine) was given by the mouth in powder form, one tablet, containing 0.1 gramme, being given three times a day for five consecutive days. To two cases, however, it was administered in gelatine capsules. No other drug was given except a light purgative whenever necessary. No restrictions regarding diet were observed. Daily examinations of blood were carried out for malaria parasites during the course of treatment, and a rough estimate of the number of parasites was also made wherever possible.

After the completion of the course the patients were carefully observed in the hospital for a fortnight, daily examinations of the blood being made for malarial parasites. Cultural examinations of the blood for malarial parasites were made where thin and thick films were negative.

Details of eight cases are given in the table. A study of the table will show that the

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of trained dispensers would be occupied in preparing a large number of doses. Against this, tetrachlorethylene requires no excipients nor capsules and it can be rapidly and accurately measured by anyone with ordinary intelligence but with no special training as a dispenser*. A final advantage of tetrachlorethylene, according to our method of treatment, is that it is mixed directly with the dose of purgative, shaken up and given immediately in a single dose, whereas thymol is given in one or two portions, which are followed in an hour or two by the purgative, so that the time taken to complete the treatment with this drug is much greater than that occupied in giving tetrachlorethylene.

Accordingly our final conclusion is that tetrachlorethylene is a better drug for the treatment of hookworm infection on the grounds of lower toxicity, lower cost, greater ease of dispensing, less time taken in completing a treatment, and greater efficiency.

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*An accurate and efficient measure for dispensing tetrachlorethylene is an old-fashioned type of hypodermic syringe of 5 c.cm. capacity, which has a screw-nut on the plunger-bar to limit the excursion of the plunger so that any desired amount of liquid less than 5 c.cm. in volume can be automatically measured. In the present instance the screw is adjusted so that only 4 c.cm. can be drawn into the syringe. Used without the needle attached, accurate doses can be measured in this way and expelled into already prepared doses of the purgative with the greatest rapidity.

TABLE

Number	Race, Sex and Age	Findings of parasites before treatment			Findings of parasites during and after treatment								Duration of fever in days after beginning of treatment	Remarks
					2nd day		3rd day		4th day		5th day			
		Species	As.*	Sex.	As.	Sex.	As.	Sex.	As.	Sex.	As.	Sex.		
1	E., M., 38	M T	Sc.	0	0	0	0	0	0	0	0	0	1	
2	H., M., 30	B T & M T	1,000	0	1,000	0	200	Cr.	Sc.	Cr.	Sc.	Cr.	3	Crescents persisted.
3	O.C., M., 22	B T	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	0	0	0	0	3	
4	I.Ch., M., 3	M T	900	Sc.	500	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	4	1/3 the adult dose given for seven days. Asexual forms disappeared on the sixth day. Crescents persisted.
5	H., M., 20	M T	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	2	Induced malaria.
6	H., M., 32	M T (Rings).	Sc.	0	Sc.	0	0	0	0	0	0	0		Temperature persisted, chronic cough.
7	O.C., F., 12	M T	Sc.	0	Sc.	0	0	0	0	0	0	0	2	Drug given for four days. No relapse within six weeks.
8	H., M., 22	B T	1,750	450	650	350	950	225	Sc.	0	0	0	3	No relapse within nine weeks.

Note.—The figures given, indicate parasite per 500 leucocytes.
Sc. indicates 'scanty', *i.e.*, less than 200 per 500 leucocytes.
Cr. indicates scanty crescents.
* As. = Asexual forms.

temperature came down to normal within one to four days and the peripheral blood was free from parasites within two to five days. The drug destroys all the forms of malaria parasites excepting the gametocytes of *P. falciparum*. Its action closely resembles that of atebrin and other acridine derivatives. Unfortunately, we had no case of quartan infection in the hospital during the period of this investigation. Rigors were seldom observed on the third day of the administration of this drug. In mild cases of benign tertian infection, if treatment with this drug was started on the day of the rigor, the next rigor was sometimes manifested in the form of a chilly sensation only. The effects of the drug on blood pressure, pulse rate and respiration were recorded; no marked changes were noticed. Haffkinine (acriquine) was mostly excreted by the kidneys and appeared in the urine on the second day of its administration, and traces of it were detected up to 25 days or even longer. A slight yellow tinge, which passed off after a few days, developed in the skin of some of the cases. There was rapid reduction in the size of the spleen in cases of acute infection, but in long-standing cases where the spleen was hard the decrease in size was more gradual and the organ often took a considerably longer time to come back to its normal size. In spite of the fact that Haffkinine persisted in the body for a fairly long time, no marked untoward symptoms were noticed. One or two cases complained of slight pain or a sensation of uneasiness in the epigastric region and loss of appetite, but these symptoms passed off with the stoppage of the medicine.

Summary and conclusions

(1) Haffkinine or 'acriquine', an acridine derivative prepared in India, is an effective drug in the treatment of Indian strains of malaria. The drug is effective in doses of 0.1 gramme three times a day, the course lasting for five days and taking a total of 1.5 grammes of the drug for the cure.

(2) Haffkinine (acriquine) in this small series of cases appeared to behave in the same way as atebrin would have done.

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