Original Articles

A COMPARATIVE STUDY OF THE ACTION OF ATEBRIN AND ATEBRIN-PLASMOCHIN COMBINATION ON INDIAN STRAINS OF MALARIA

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DURING the last decade a number of compounds have been synthesized for the treatment of malaria and of these, plasmochin and atebrin have proved to be the most effective and are being extensively used. The main action of plasmochin is on the sexual forms of *P. falciparum* while atebrin, like the cinchona alkaloids, acts on the asexual forms of *P. falciparum* and on both sexual and asexual forms of *P. vivax* and *P. malariæ*. In the case of Indian strains the quantity of plasmochin, necessary to remove the crescents effectively, has been worked out to be 0.04 gm. to 0.06 gm. distributed over a period of two to three days while the usual effective dose of atebrin is 0.1 gm. three times a day for five consecutive days. Although the production of these synthetic remedies is a distinct advance in the therapy of malaria, the problem of prevention of relapses still remains unsolved.

The action of plasmochin has been fully investigated by various workers and although the drug has been shown to act chiefly on the sexual phase of the malarial parasites, a strong belief still exists in some quarters, that plasmochin has marked curative properties in the same way as atebrin or the cinchona alkaloids, and that it is even effective in preventing relapses. Green, Freiman and Stern (1929) have treated malaria with plasmochin alone, but our experience with Indian strains is that the dosage required to produce any obvious effects is likely to produce marked toxic symptoms.

In the attempt to effect a permanent cure for malaria, the medical profession in this country have been using plasmochin combined with either quinine or atebrin. Tablets containing these combinations in various proportions have been put on the market by reliable firms, as there is a great demand for them in various parts of the world. Certain advantages are claimed for these combinations, for example in malignant tertian infection by acting on the gametocytes they are said to shorten the duration of treatment and reduce to a considerable extent the chances of transmission of malaria to others. Often plasmochin has been used in large doses and for prolonged periods in these combinations and toxic symptoms have resulted in the form of epigastric pain, cyanosis, cardiac arhythmia, yellow coloration of the body, etc.

A study of the reports of different workers leaves no room for doubt as to which drug is responsible for the production of the toxic effects. Plasmochin has been unanimously declared a toxic drug and its administration in large doses and for prolonged periods has undoubtedly produced severe toxic effects. Occasionally even small doses are liable to produce gastric pain or cyanosis or both. Chopra and Chaudhuri (1935) have quoted cases showing the possibility of the toxicity of plasmochin being enhanced by its combination with atebrin.

The view that plasmochin acts also on the asexual stages of malarial parasites and that its combination with atebrin may increase the activity of the latter drug in preventing relapses, was utilized by Messrs. Bayer-Meister Lucius in preparing the atebrin-plasmochin dragées each of which contains 0.1 gm. of atebrin and 0.0033 gm. of plasmochin. The idea underlying this combination is to obtain the effects with minimum doses of plasmochin in order to avoid the production of toxic symptoms. The dose of plasmochin has been kept within safe limits so that, even if it fails to produce any reduction in the relapse rate, it will carry on its crescenticidal action without causing undesirable symptoms. These dragées are coated in such a way that they are not acted upon by the gastric juice and disintegration usually occurs lower down in the intestine. In this paper we have given the result of a preliminary investigation regarding the effect of these atebrin-plasmochin dragées on Indian strains of malaria as compared with atebrin by itself. The studies in connection with this combination were carried out to determine the effects :

(1) on the sexual and asexual forms of the parasites and the time taken for their complete disappearance from the peripheral blood,
(2) on the relapses,
(3) on the splenic enlargement,
(4) on the function of liver, and
(5) to note any untoward symptoms produced by this combination.

The dragées were tried on a series of 54 cases in the Carmichael Hospital for Tropical Diseases and the effects were compared with those obtained on a previous series of cases treated with atebrin alone. Patients suffering from malaria were admitted under the senior author and a thorough physical examination was conducted immediately after admission. Thin and thick blood films were carefully examined and in some cases a rough estimate of the number of malarial parasites per c.mm. was also made. Except in urgent cases, the anti-malarial treatment was not commenced until the parasites were properly identified and the parasitic

counts were fairly constant for two or three consecutive days. Daily examination of blood during this period enabled us to watch the progress of the cases and gave us information regarding the intensity of the infection. If the parasites in the peripheral blood were scanty, these were allowed to increase till the counts were fairly high and the rigor and other symptoms were fairly pronounced. Whenever possible, sugar tolerance and van den Bergh's tests were performed both before and after the course of treatment, in order to find out if atebrin and plasmochin, when given in combination, produce any damaging effect on the function of the liver.

When all these preliminary investigations were completed the drug was given by the mouth, one dragée (containing 0.1 gm. of atebrin and 0.0033 gm. of plasmochin) three times a day for five consecutive days being the usual dose for an adult. No other drug was given except a light purgative whenever necessary. As regards diet, only the usual restrictions for a febrile condition were observed. During the course of treatment daily examination of the blood was carried out and, whenever possible, a rough estimate was also made of the number of parasites per c.mm. of blood.

After the completion of the treatment, the patients were carefully observed in the hospital for at least a fortnight and daily examinations of blood for malarial parasites were conducted during this period. If thick and thin films showed no parasites, cultural examinations of the blood were finally made before the patients were discharged. If routine laboratory examinations revealed any other infection, *e.g.*, dysentery, helminthiasis, etc., these were treated during the period of observation.

TABLE I

The relationship between the percentage of cases and the number of days required for complete disappearance of parasites from the peripheral blood after the commencement of the treatment

Species of parasites	Complete disappearance of parasites from peripheral blood												Remarks
	Number of cases studied		On the 3rd day in percentage of cases studied		On the 4th day in percentage of cases studied		On the 5th day in percentage of cases studied		On the 6th day in percentage of cases studied		In more than 6 days in percentage of cases studied		
	A+P	A	A+P	A	A+P	A	A+P	A	A+P	A	A+P	A	
B.T. ..	20	11	28.5	54.6	42.9	36.4	19.0	9.0	4.8	..	4.8	..	
M.T. ..	19	18	31.9	11.1	18.2	33.3	13.6	11.1	22.8	..	9.1	44.4	
Quartan ..	4	5	..	20.0	..	80.0	50.0	..	..	..	50.0	..	In one case the parasites were found in the peripheral blood even on the 8th day after commencement of treatment.
Mixed B.T. and M.T.	7	3	..	..	57.3	33.3	14.2	..	14.2	..	14.2	66.6	In one case B. T. disappeared on the 8th day. Recurrence of the same infection one month after the course of treatment.

A = Atebrin. P = Plasmochin.

TABLE II

The comparative efficacy of the drug on sexual and asexual forms of different species

Species of parasites	Sexual forms						Asexual forms					
	Number of cases where present		Percentage of cases where they disappeared within 4 days		Percentage of cases where they disappeared in more than 4 days		Number of cases where present		Percentage of cases where they disappeared in 4 days		Percentage of cases where they disappeared in more than 4 days	
	A+P	A	A+P	A	A+P	A	A+P	A	A+P	A	A+P	A
B.T. ..	10	7	90.0	100.0	10.0	..	19	11	70.0	100.0	30.0	..
M. T. ..	12	9	41.7	11.2	49.5	88.8	19	18	52.6	100.0	47.4	..
Quartan ..	3	4	33.3	100.0	66.6	..	4	5	0.0	100.0	100.0	..

A = Atebrin. P = Plasmochin.

TABLE III

The relationship between the parasite count and the number of days required for disappearance of parasites

Species	WITH A + P		WITH A	
	Parasite count on the day of commencement of treatment	Number of days required for complete disappearance of parasites from peripheral blood	Parasite count on the day of commencement of treatment	Number of days required for complete disappearance of parasites from peripheral blood
B. T. ..	(1) 12,600	3 days	(1) 10,020	4 days
	(2) 22,000	2 „	(2) 16,820	3 „
	(3) 18,000	2 „	(3) 30,000	2 „
	(4) 7,500	3 „	(4) 28,000	1 day
	(5) 8,500	2 „	(5) 21,400	3 days
	(6) 4,720	5 „	(6) 9,840	2 „
			(7) 10,000	3 „
M. T. ..	(1) 7,000	4 days	(1) 9,240	more than 6 days
	(2) 15,400	2 „	(2) 3,840	„ „ 6 „
	(3) 920	3 „	(3) 14,200	only 4 „
	(4) 3,500	2 „	(4) 128,000	more than 6 „
	(5) 880	5 „	(5) 13,000	6 „
Quartan ..	(1) 560	8 days	(1) 3,520	3 days
	(2) 950	4 „	(2) 1,000	3 „
			(3) 800	2 „
			(4) 2,400	3 „

TABLE IV

The function of liver before and after treatment

No.	Species	Liver function test before treatment	Liver function test after treatment
1	B. T.	Slightly defective	Not done.
2	B. T.	Normal	Normal.
3	M. T.	Slightly defective	Not done.
4	M. T.	Normal	Normal.
5	M. T.	„	„
6	B. T. M. T.	Doubtful	Not done.
7	B. T.	Normal	Slightly defective
8	Quartan	„	„ „
9	M. T.	„	Not done.
10	Quartan	Doubtful	„ „
11	M. T.	Normal	„ „
12	M. T.	„	„ „
13	M. T.	„	Normal.
14	B. T. M. T.	Defective	Defective.

Results and discussion

Chopra, Das Gupta and Sen (1933) have studied the effects of atebrin alone, on the Indian strains of malaria; the results obtained in that series have been analysed for purpose of comparison along with those obtained with atebrin-plasmochin dragées.

A perusal of table I will show that the atebrin-plasmochin combination acts both on the asexual and the sexual stages of all the three species and that the time taken by *P. falciparum* and *P. vivax* for their complete disappearance is usually two to five days. A small percentage, however, showed a delayed response, the parasites disappearing six days after the commencement of treatment. In cases of infection with *P. malariæ*, the destruction occurs comparatively slowly; 50 per cent of the cases took more than six days for the parasite to disappear from the peripheral blood. The delayed response shown by some of the cases may be ascribed to two factors. In the first instance, some of these cases were chronic sufferers with an enlarged spleen; the blood was deficient and a lowered activity of the gastro-intestinal tract existed. It is therefore likely that the absorption of the drug may have been hampered and the concentration in the blood necessary to produce the desired effect was not attained. The second factor responsible was that some of these patients were young children and care had to be exercised to avoid untoward symptoms and too small doses were perhaps given.

A comparative study of the effects of atebrin-plasmochin dragées and atebrin alone shows that, in cases of infection with *P. vivax*, the disappearance of the parasites by both methods of treatment is complete in the majority of the cases within four days, whereas with malignant tertian infection the combination removes them in a shorter time than atebrin alone. The reason of this will be obvious from a perusal of table II which shows that atebrin does not act on the crescents and consequently the sexual forms persist even after the course of treatment is over. In quartan malaria, atebrin alone produces even more rapid action than the atebrin and plasmochin combination.

Table II gives an idea of the comparative efficacy of these dragées on the asexual and the sexual forms of the different species. In benign tertian infection, the sexual forms are more rapidly affected than the asexual, but in the case of malignant tertian, this treatment produces practically the same effect on both forms. As regards quartan, the number of cases was unfortunately too small to enable us to form an accurate conclusion; the gametocytes seem to disappear more quickly than the asexual forms. The comparatively rapid destruction of the benign tertian gametocytes may be partly explained by their tendency to spontaneous disappearance.

A comparison of the effects of atebrin alone and with the combination dragées shows that atebrin produces a more rapid action both on the asexual and sexual forms of *P. vivax*, but in the case of *P. falciparum*, although it removes the asexual forms in the majority of cases within a short time, the sexual forms are rarely touched and persist even after the course of treatment is completed. In the case of *P. malariæ*, atebrin alone appears to be as effective or even superior to the combined dragées with regard to their action on both the asexual and sexual forms.

Table III shows that there is no relationship between the parasite count and the number of days required for the complete disappearance of the parasites. The explanation may be that, in the concentrations in the body after administration of therapeutic doses, the drug may not possess a direct lethal action on the parasites and their destruction may be the outcome of certain processes in the body in which the reticulo-endothelial system probably plays an important part. This question is now being studied and the results will be published in due course. A perusal of this table will show that both the drugs behave in more or less the same way with regard to the relationship between the parasite count and their disappearance from the peripheral blood.

Relapses.—Out of a total of 39 cases treated with atebrin alone, five apparently relapsed while still under observation in the hospital. Out of 54 cases treated with the combination only two (one *P. falciparum* and one *P. vivax*) relapsed. This shows that the relapse rate is 12.5 per cent in case of atebrin and 3.7 per cent in case of the combination. The series of cases is very small, but in view of the fact that these trials were carried out under fully controlled conditions, the results are worthy of note.

Spleen.—So far as the effects on the spleen are concerned a soft spleen rapidly contracts when the patient is put on either treatment and the fever subsides. No difference could be observed in the case of the two treatments in this connection. The hard spleen of chronic malaria shows very little alteration.

Effect on the liver function.—Lævulose tolerance and van den Bergh's tests were performed on a small series of 14 cases. A perusal of table IV will show that, out of these 14 cases, 5 showed an already defective liver. Of the remaining 9, the tests after the course of treatment could be done on 6 only, out of which 4 showed normal liver, and in 2 cases, the liver function was found to be slightly defective after the treatment. Further work is being carried on in this connection but from the small number of examinations that have been done we have formed the opinion that in ordinary healthy patients, who suffer from an attack of malaria, the administration of atebrin or atebrin-plasmochin dragées has no marked effect on the liver.

Untoward symptoms.—In the majority of the patients treated in this series, we have not met with any serious untoward symptoms. In some cases toxic symptoms undoubtedly did develop. One patient with malignant tertian infection developed the usual toxic effects after eleven doses of atebrin and plasmochin and looked cyanosed and collapsed. Stimulants had to be given and atebrin and plasmochin dragées had to be replaced by quinine. In another case of malignant tertian infection and in one of benign tertian, precordial distress was felt after the use of the dragées and they had to be stopped in the middle of the course of treatment. Two patients complained of slight epigastric pain and flatulence but could complete the course of treatment. There was a diabetic in our series who showed a marked rise in his blood sugar after the course of treatment. Yellow pigmentation of the whole body was observed in quite a large number of patients. The pigmentation disappeared in the course of a few days in most cases but in some, slight yellow coloration persisted even up to the time of discharge from the hospital. From a careful study of the two series of patients we have formed the opinion that toxic coloration is somewhat more frequent with the combination than with atebrin alone.

Summary and conclusions

(1) Comparative studies have been carried out in a small series of cases on the therapeutic effects produced by atebrin alone and atebrin-plasmochin dragées (containing atebrin 0.1 gm. and plasmochin 0.0033 gm.).

(2) In cases of benign tertian and quartan malaria the combination of the two drugs is not more effective than atebrin alone in so far as the time of disappearance of the parasites from the blood is concerned. In the case of malignant tertian infection, however, the combination appears to be more effective and the parasites disappear more rapidly from the peripheral circulation.

(3) With regard to the relationship between the number of parasites and their disappearance from the peripheral circulation, atebrin alone

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ROLE OF INFECTION IN THE ÆTIOLOGY OF INFANTILE CIRRHOSIS OF THE LIVER

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SINCE the first description of this disease by Dr. B. C. Sen (1887) in 1887, at a meeting of the Calcutta Medical Society different theories have been advanced from time to time by various observers about the underlying causes, but our knowledge does not seem to be much advanced. Dietetic errors in children and bad hygienic conditions are supposed to be the most important ætiological factors. Early observers agree about them and they have been corroborated by many physicians of modern times. But there is no agreement about the particular form of diet which is prone to give rise to the symptoms. Thus Ghosh (1887), Coomar and Simpson (1888) and Bose (1890) ascribed the cause to irregular and overfeeding of undiluted, hard-boiled cow's milk along with bad hygienic surroundings. Mackenzie (1895), in North Canara, attributed it to giving irritating foods, seasoned with aromatics, early administration of starch, and the mother taking strong decoction of black pepper; but mothers are not accustomed to take these things in Bengal where the disease is so prevalent. Ghosh (1895), analysing 400 cases, ascribed the cause to mothers suckling their babies during pregnancy, bottle feeding of unwholesome milk, irregularity of feeding and overfeeding. Gibbons (1890) attributed it to giving unwholesome food, especially early administration of starch in large quantities. In cases where the child was having mother's milk alone, he ascribed the cause to the unhealthy state of the mother. Green-Armytage (1926) incriminates, among other factors, the excess of fat in cow's milk, whereas Gothoskar (1931) observes that the essential cause of this disease is starvation of infants, especially starvation in fats and sugar. Bhattacharjee (1931) reports that in many of his cases the fault of the diet was excess of sugar and deficiency of proteins. Castellani and Chalmers (1919) and also Manson-Bahr (1925) thought that it might be a form of infantile kala-azar. Against this latter view it may be said that Mukherjee (1928) made a routine examination of the blood of 292 cases of 'infantile liver', and no sign of kala-azar was present in any of his cases. The present author also examined the blood of some of his cases of 'infantile liver' for kala-azar, and he could find no sign of this disease in any of them. About alcoholism, syphilis, and malaria in parents, most of the observers agree with Gibbons (1890) that these have got nothing to do with the disease, though Iyer (1927) mentions that in Southern India syphilis is often found amongst the parents of the children suffering from this disease. Tirumurti and Radhakrishna Rao (1934) and Radhakrishna Rao (1935) regard the disease as a form of subacute toxic cirrhosis. Pandalai (1934) also regards it as a form of gastro-intestinal toxæmia resulting from early faulty feeding and a congenitally insufficient liver with inadequate defence powers.

Heredity.—It has been pointed out by Sen (1890), Ghosh (1887), Gibbons (1890) and others that the disease shows a familial tendency in many cases like the Hanot's type of cirrhosis.

The question arises whether dietetic error is the sole causative factor in the production of biliary cirrhosis in children. Simple enlargement of the liver due to dietetic error is often

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and atebrin-plasmochin dragées behave in the same way.

(4) The relapse rate is definitely lower in cases where the combination of the two drugs is used than with atebrin alone, in all forms of infections.

(5) There appears to be no difference in the two so far as the reduction of the size of the spleen is concerned.

(6) The combination of the two drugs is more toxic than atebrin alone.

(7) Distinct advantage can be gained by treating cases of malignant tertian infection with the combination dragées especially when the sexual forms are present. In the case of benign tertian and quartan infections they appear to have no marked advantage.

It is fully realized that the series of cases dealt with in this paper is very small and that the conclusions are only provisional. We are grateful to Messrs. Bayer-Meister Lucius for supplying the dragées free of charge for these trials. The work is being continued with the combination of the two drugs with a larger dose of plasmochin (atebrin 0.1 gm. and plasmochin 0.005 gm.).

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