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Whole Article

THE RELATIVE EFFICIENCY OF QUININE AND QUINIDINE IN THE TREATMENT OF MALARIA

BY

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INTRODUCTION.

IN the year 1866 the Madras Government appointed a commission to examine the respective efficiency of quinine, quinidine, cinchonine, and cinchonidine. Judging from clinical observations, the commission found that all four of the alkaloids are of use in the treatment of malaria, and that there is very little difference in their remedial value (Dymock, 1891). Fifty years later, Acton (1920), as the result of his researches at Dagshai, concluded that quinidine and cinchonidine are of outstanding merit in effecting the permanent cure of benign tertian malaria. Two years ago we made a comparative test of quinine and quinidine, in this laboratory, by treating twenty men with quinine sulphate and the same number with quinidine sulphate (Fletcher, 1923). The average weight of these men was about 46 kilogrammes (101·5 lb.), and each of them was given the same dose of five grains, twice a day. The quinine was obtained from the Bandoengsche Kininefabriek of Java, and the quinidine from Messrs. W. Martindale of London. The blood of each patient was examined daily, and from the results of the investigation we concluded that quinidine was quite as effective as quinine in the treatment of malaria.

At the request of the Medical Research Council we have repeated these investigations, employing purified samples of the bisulphates of quinine and quinidine which had been specially prepared for the Council by Messrs. Howards and Sons. The results of this second investigation were concordant with those of the first, and have confirmed our former conclusion.

DETAILS OF THE PRESENT INQUIRY.

Our observations were made on seventy patients who had been admitted on account of malaria to the District Hospital at Kuala Lumpur, and for this privilege we are indebted to Dr. E. A. Smith, the medical officer in charge of that institution. Forty-eight of the patients were Tamils and twenty-two were Chinese. They were all immigrant labourers employed on rubber estates and tin mines. Only eight of them had been less than one year in the Malay States, thirty had been in the country for more than five

years, and all but nine had suffered from repeated attacks of malaria. The investigation was made during December, 1923, and the first three months of 1924. At that time malaria was not prevalent; the few patients who were admitted to hospital were suffering from a mild form of the disease, and there was an unusually large proportion of quartan infections. The series of seventy patients comprised sixteen cases of benign tertian fever, twenty-four subtertian, eight mixed tertian, and twenty-one quartan; three of the latter were complicated by an additional subtertian infection.

The patients were not selected in any way; all who came into hospital with malaria were treated with the purified drugs until the supply was exhausted. Seventy-two patients were numbered consecutively on their admission to hospital. The first patient and all those bearing odd numbers were given quinine; those with even numbers (i.e. the second and alternate patients) were given quinidine. Two of the men in the quinine group absconded and therefore were not taken into account, consequently there remained thirty-four treated with quinine and thirty-six treated with quinidine.

It is not practicable to keep the ordinary Asiatic hospital patient under observation and shielded from re-infection with malaria for a period sufficiently long to gauge efficiency of different drugs in preventing relapses, and the Council, recognizing this, desired that the respective values of quinine and quinidine should be estimated, by comparing their immediate effect upon the patient, the parasite, and the fever. They suggested that the period of special observation and examination should be limited to five days, but in nineteen of the quartan and five of the tertian cases in our series this was extended to ten days or longer. The Council supplied a printed form for the purpose of recording the details of each case and, with slight alterations which were made to suit local conditions, this form was used throughout.

As the Council directed, the dose administered to each patient was proportionate to his weight. The drugs were employed in small doses because we knew, from former experience, that there was little or nothing to choose between them in respect of their power to clear the blood of malaria parasites, and any slight superiority of one over the other would be masked by the use of large quantities. Consequently we selected a dose of 0·1 gr. for each kilogramme of body weight, and gave this amount twice a day to all except eight of the quartan cases, who were given double doses. The average weight of the patients was 48·2 kgm. (106 lb.) In the quinine group it was 45 kgm., and in the quinidine group it was 50 kgm. The average dose in the first group was therefore 4·5 gr., twice a day, and in the second group, 5 gr.

The quinine and quinidine were given dissolved in plain water; one dose in each ounce. We weighed the patients and we compounded and administered their medicine ourselves. The latter was given at 9 o'clock in the morning and 4 o'clock in the afternoon. The effect would have been better, probably, if the evening dose had been given at a later hour, with a shorter interval between it

and the dose on the following morning, but 9 and 4 o'clock were chosen because they were the most convenient hours.

Blood-films were stained with Leishman's stain and examined twice a day, at the time the quinine was administered. All the films were made and stained by my assistant, Mr. Kandiah; the examinations were made by Mr. Kandiah and myself. The number of microscope fields examined and the number of parasites found were noted in each case, and in the patients' records the result of each examination was written as a vulgar fraction with the number of parasites as the numerator and the number of fields examined as the denominator. This is admittedly a rough method; but, as all the slides were prepared by the same hand, it is of use for purposes of comparison.

A sample of urine was collected when each dose was given, and it was examined for albumin and quinine; at the same time an inquiry was made as to the presence of any toxic symptoms produced by the drugs which were being administered.

The Effect of Treatment on the Temperature.

The temperature did not rise above 100° F. in any of the patients after they had completed three days' treatment, nor was it above normal, in any instance, after the fifth day.

In the quinine group, consisting of thirty-four men, the temperature was not above normal after the third day, except in five. These five comprised two cases of benign tertian fever, numbers 44 and 65, in which the temperature was 99° F. on the fifth day—from causes other than malaria—and three cases of quartan, numbers 43, 59, and 63, in which the temperature was between 99° F. and 100° F. on the fifth day. There was no example of persistent fever in the quinine group.

The results were even better in the group of patients who were treated with quinidine. The temperature was normal after three days' treatment except in three quartan cases, numbers 12, 28, and 33. In the first, it was normal after the morning of the fourth day; in the other two, it was 98·6° F. in one instance, and 99° F. in the other, on the fifth day; but it did not rise above normal during the next five days while they were kept under observation.

The Effect of Treatment on the Parasites.

Asexual parasites usually disappear before the fifth day when quinine is administered in adequate doses. In the series of patients treated with quinine bisulphate there were ten (three subtertian, two mixed tertian, and five quartan) who had parasites in their blood on the fifth day or later; in the quinidine series there were seven, all quartan.

If no patients with quartan malaria had been included in this investigation, there would have been a notable difference in the results; for, in that case, the men who had trophozoites in their blood, after five days' treatment, would have numbered only five in the quinine group, and there would have been none at all in the

quinidine group. On the other hand, if these observations had been made at a time when severe subtertian malaria was present in epidemic form, it is probable that with such small doses as we employed, a few trophozoites would have remained after four or five days' treatment. For a comparative test of the two drugs, the mild cases which were available when we made our investigation, and which rendered it possible to use these small doses without fear, were particularly suitable.

When the first doses were given, there were thirty-four patients in the quinine group (six benign tertian, thirteen subtertian, five mixed tertian, and ten quartan), and thirty-six patients in the quinidine group (ten benign tertian, twelve subtertian, three mixed tertian, and eleven quartan).

At the time the fifth dose was given, twenty-nine patients in the quinine group still harboured asexual parasites, but in the quinidine group only seventeen remained infected.

At the tenth dose, trophozoites were found in six patients belonging to the quinine group (one subtertian, two mixed tertian, and three quartan) and in five of the quinidine group, all of the latter being quartan infections.

At the fifteenth dose there were two patients with trophozoites in the quinine group (numbers 47 and 55, one a quartan and the other a mixed tertian); but in the quinidine group all the patients were free from asexual parasites. The trophozoites disappeared from number 47 after the fifteenth dose, and from number 55 after the nineteenth.

The results of treatment with quinidine were, therefore, a little better than with quinine. No asexual parasites, other than quartan, were found in the quinidine series subsequent to the seventh dose, and no quartan parasites, except gametocytes, after the fourteenth.

TABLE I.

QUININE BISULPHATE.

Showing the last dose at which fever and parasites were present in each case.

Case Number.	*Type of disease.*	*Last dose at which fever present.*	*Last dose at which parasites present.*
3	Quartan	6	6
9	,,	1	5
19	,,	2	4
21	,,	3	8
25	,,	2	9
27	,,	6	8
39	,,	2	10
47	,,	4	15
49	,,	3	13
51	,,	6	9
1	Benign tertian	1	2
11	,, ,,	4	6
35	,, ,,	6	3
41	,, ,,	5	5
45	,, ,,	4	5
65	,, ,,	9	6
7	Subtertian	3	5
13	,,	4	5
17	,,	4	5
23	,,	2	4
29	,,	4	9
33	,,	4	6
37	,,	1	5
43	,,	9	7
53	,,	4	6
59	,,	9	12
63	,,	11	9
67	,,	4	6
69	,,	2	7
5	Mixed tertian	15	13
15	,, ,,	2	4
31	,, ,,	4	6
55	,, ,,	5	19
57	,, ,,	6	6

TABLE II.

QUINIDINE BISULPHATE.

Showing the last dose at which fever and parasites were present in each case.

Case Number.	*Type of disease.*	*Last dose at which fever present.*	*Last dose at which asexual parasites present.*
2	Quartan	5	4
6	,,	2	12
8	,,	2	10
12	,,	7	9
26	,,	4	5
28	,,	10	14
30	,,	10	9
32	,,	1	8
38	,,	6	7
40	,,	1	11
48	,,	4	11
4	Benign tertian	1	2
24	,, ,,	1	4
34	,, ,,	2	3
52	,, ,,	2	4
56	,, ,,	3	6
60	,, ,,	3	3
62	,, ,,	3	3
64	,, ,,	3	3
68	,, ,,	2	3
72	,, ,,	4	3
16	Subtertian	4	4
18	,,	2	2
20	,,	4	4
22	,,	1	1
36	,,	6	6
42	,,	4	7
44	,,	3	5
46	,,	5	6
50	,,	1	4
54	,,	4	4
66	,,	2	4
70	,,	6	5
10	Mixed tertian	1	3
14	,, ,,	4	4
58	,, ,,	2	5

Details of Cases in which Asexual Parasites did not disappear before the Fifth Day of the Treatment.

Tertian.

Case 5. This patient, aged 20, weighed only 38·6 kgm., or five stones. He was suffering from a rather mild attack, the result of a mixed tertian infection, and was given 3·9 grains of quinine twice a day. Asexual parasites were not found after the fifteenth dose.

Case 55. He was a boy aged 16, who was given 4 grains of quinine twice a day. There was no vomiting or albuminuria, but the absorption of quinine was not good. There was no fever after the third dose, and the number of parasites in a hundred fields was reduced from twenty-eight to four or five, but at this figure they remained until the nineteenth dose, when they finally disappeared.

Cases 29, 63, 59. These three were subtertian cases under treatment with quinine. Trophozoites were present up to the ninth dose in the first two, and until the twelfth dose in number 59. The absorption of quinine was fairly good, there was no albuminuria, and number 29 was the only one who vomited.

Quartan.

Cases 25, 51, 39 were all under treatment with quinine, and all had asexual parasites in their blood at the time of the ninth or tenth dose, but not subsequently.

Case 47 was given quinine at the rate of 0·2 grain per kgm. in each dose or 9·8 grains twice a day. He did not vomit, but albumin was present in his urine throughout the course, and the absorption of quinine was poor. There was no fever after the fourth dose, but trophozoites were present at the time the tenth dose was given and again at the twelfth and fourteenth doses.

Case 49 was also given 0·2 grain of quinine per kgm., or 10·9 grains twice a day. In this case there was albuminuria throughout the course of treatment, and he vomited on one occasion. The absorption of quinine was good. Asexual parasites were found at the eleventh and thirteenth doses, but not later.

Cases 12 and 30 were both in the quinidine series. In neither of them did the temperature rise above normal after the seventh dose, but in each case a few asexual parasites were found at the time of the ninth dose.

Cases 6, 8, 40, and 48 were all under treatment with quinidine. In none of the four did the temperature rise above normal after the first day's treatment, but asexual parasites did not disappear

entirely until the twelfth, tenth, eleventh, and eleventh doses respectively.

Case 28 was also a patient in the quinidine group and, as is common in quartan cases, there was moderate albuminuria. The absorption of quinidine was fair and there was no vomiting, but trophozoites were present in small numbers at the ninth examination and again at the fourteenth (one parasite in five hundred fields), but not subsequently.

TABLE III. *Showing the last dose at which asexual parasites were found. The figures are the case numbers entered opposite the dose at which parasites were last found. Figures printed in ordinary type denote the quinine series, those in italic the quinidine.*

	Benign tertian cases.	Subtertian cases.	Quartan cases.	Mixed tertian cases.
1st dose		*22*		
2nd ,,	1, *4*	*18*		
3rd ,,	35, *72*, *68*, *64*, *62*, *60*, *34*			*10*
4th ,,	*52*, *24*	23, *66*, *54*, *50*, *20*, *16*	19, *2*	15, *4*
5th ,,	41, 45	7, 13, 17, 37, *70*, *44*	9, *26*	*58*
6th ,,	11, 65, *56*	33, 53, 67, *46*, *36*	3	31, 57
7th ,,		43, 69, *42*	*38*	
8th ,,			21, 27, *32*	
9th ,,		29, 63	25, 51, *30*, *12*	
10th ,,			39, *8*	
11th ,,			*48*, *40*	
12th ,,		59	*6*	
13th ,,			49	5
14th ,,			*28*	
15th ,,			47	
16th ,,				
17th ,,				
18th ,,				
19th ,,				55
20th ,,				

QUARTAN INFECTIONS.

With the exception of three cases in the quinine series all tertian trophozoites disappeared from the blood before the fifth day of treatment. Quartan parasites are more resistant than tertian, and in twelve out of a total of twenty-one cases asexual parasites withstood more than four days' treatment. This is only to be expected if the hypothesis be accepted that the cinchona alkaloids exert their specific effect on the parasite at the time of sporulation. The fever did not persist with the parasites, but rapidly responded to treatment, and in every case the temperature was normal by the fourth day.

The quartan gametocyte is more resistant to quinine than the benign tertian, but less resistant than the subtertian crescent. In most cases quartan gametocytes persisted for several days after the asexual forms had disappeared. For instance, in patient No. 35, no

asexual parasites were seen after the ninth dose, but gametocytes were found up to the twenty-eighth; in cases 19 and 32 gametocytes persisted eleven doses longer than the trophozoites, and in cases 3 and 39 for eight doses longer.

Doubling the dose did not appear to hasten the disappearance of the quartan parasites. Thirteen patients (Nos. 2, 3, 6, 8, 9, 12, 19, 21, 25, 26, 27, 30, 32) were given 0·1 grain per kgm. and eight (Nos. 28, 38, 39, 40, 47, 48, 49, 51) were given 0·2 grain per kgm. Four of the first group and seven of the second had asexual parasites for more than four days, and gametocytes were present, on an average, up to the sixteenth dose in both groups.

In subtertian malaria it is very easy to distinguish the gametocytes from the asexual forms; in benign tertian it is not a matter of importance, because all the parasites disappear after a few doses; but in quartan malaria we find it very difficult sometimes to be quite certain whether a given parasite is a trophozoite or a gametocyte, especially when only one is found in two or three slides. On this account we prolonged the period of observation in those cases where gametocytes were present, in order to see if trophozoites or schizonts would appear, and thus we were able to ensure the correctness of our diagnosis.

Toxic Symptoms due to the Drugs.

The doses of quinine and quinidine were so small that they caused no toxic symptoms or by-effects. There was no instance of deafness, vertigo, amaurosis, tremors, headache, or diarrhoea due to the drugs. Six of the patients in the quinine group were vomiting when they were admitted to hospital, but this ceased as soon as the quinine began to take effect. Two other men on quinine treatment, Nos. 29 and 49, vomited once or twice during the course; in No. 25 this was due to bacillary dysentery, in No. 49 the cause was probably an error in diet. There were only three patients in the quinidine series who vomited: Nos. 62 and 70, who vomited after the first three or four doses, and No. 46, who vomited once after the seventh dose.

Each patient's urine was examined twice a day, with the result that albumin was found in twelve of the quinine group and fourteen of the quinidine group, on at least one occasion; but this was not due to the drugs; on the contrary, in eleven cases the albumin disappeared entirely, or almost entirely, from the urine when the parasites disappeared from the blood after a few doses of medicine (Nos. 6, 10, 18, 19, 28, 30, 40, 44, 49, 51, 69). In eight patients there was albuminuria for a single day only (Nos. 11, 21, 22, 27, 38, 45, 48, 46). Albumin was present throughout in seven cases (Nos. 3, 4, 12, 41, 46, 66, 67), but in only one patient, No. 12, was it more than a trace.

The urine was tested for the alkaloids twice a day by the addition of Mayer's reagent, and the result was noted on the patients' record form as 'nothing', 'trace', or 'cloud' according to the appearance of the precipitate.

When the records of the two groups of patients were compared it was found that the precipitate was more constant and marked in the quinidine than in the quinine group. Samples of urine, 197 in number, from patients in the quinidine group, were tested at 3 p.m., six hours after the previous dose. They all gave a precipitate and in all but three this was more than a 'trace'. Two hundred and eighteen samples from the quinine group were examined at the same time, with the result that in no less than twenty-four there was only a 'trace' and in five there was 'nothing'. At the morning examination, which was made at 9 a.m., seventeen hours after the last dose on the previous afternoon, the difference was very striking; in the quinidine group only nine, out of 189 specimens of urine, gave no reaction; but in the quinine group negative reactions were five times more frequent, and in 46 out of 217 specimens there was no precipitate on the addition of Mayer's reagent. The quinidine group received an average dose of 5 grains in accordance with the average weight; but the average dose of the quinine group was only 4·5 grains because the average weight was half a kilogramme less. Attention is drawn to this because there is a deeply rooted belief among medical men in this country that small people, or at least children, require proportionately larger doses.

SUMMARY.

Seventy-two men suffering from malaria were divided into two groups, one of which was given treatment with quinine bisulphate, and the other with quinidine bisulphate. These salts were pure samples specially prepared for the Medical Research Council. They were administered twice a day, at 9 a.m. and 4 p.m., when blood-films were examined, temperatures taken, samples of urine examined for albumin and quinine, and an inquiry made for toxic effects caused by the alkaloids.

Quinine Group. Thirty-four men were treated with quinine bisulphate. (Two of the original thirty-six absconded.) The amount given was 0·1 grain for each kgm. of body-weight, twice a day, except in six quartan cases where double this quantity was employed. The thirty-four cases treated with quinine comprised the following: benign tertian, 6; subtertian, 13; mixed tertian, 5; quartan, 10. The temperature became normal on the completion of three days' treatment, except in five cases where there was a slight rise on the fifth day. Asexual parasites disappeared from the blood before the fifth day in twenty-four of the patients. In one quartan case parasites were present until the seventh day (fifteenth dose), and in one mixed tertian case up to the tenth day (nineteenth dose), which was the longest time they persisted in any of the patients.

Quinidine Group. Thirty-six men were treated with quinidine bisulphate, 0·1 grain for each kgm. of body-weight, twice a day, except in seven quartan cases, where double this quantity was given. The thirty-six cases treated with quinidine comprised the following: benign tertian, 10; subtertian, 12; mixed tertian, 3; quartan, 11. The temperature became normal on the completion of three days' treatment, except in three quartan cases, and in these there was no rise after the fifth day. Asexual parasites disappeared from the blood before the fifth day in twenty-nine of the patients. The seven remaining were all quartan cases, and they were all clear of asexual parasites by the seventh day (fifteenth dose) of treatment.

Conclusion.

The immediate effect of quinidine bisulphate in malaria is as good as, or slightly better than, that of quinine bisulphate.

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