

LEAGUE OF NATIONS.

C.H.Malaria/214.

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HEALTH ORGANISATION.

MALARIA COMMISSION.

The Medical Director has the honour to communicate an extract of

"Notes on Totaquina".

read on December 16th, 1933, before the F.M.S. Division of the British Medical Association, by Dr. J.W. Field, J.M.R.; F.M.S., K.L. of the Institute for Medical Research, Kuala Lumpur (F.M.S.).

I.

CLINICAL OBSERVATIONS.

417 cases of malaria personally treated and recorded, with thick film blood examination and parasite counts made daily over a seven day treatment period have provided the clinical material for this enquiry. The numbers are thus sufficiently large to smooth out most of the irregularities inseparable from small scale enquiries. Approximately half of these cases were treated with Totaquina, and half under parallel conditions with quinine bihydrochloride.

The Totaquina employed was a Type II product, manufactured by Messrs. Howards, London.

Methods of administration of Totaquina.

- (a) As a solution of the bihydrochloride containing 2% of the mixed bases; prepared by dissolving 40 grammes of Totaquina in 247 c.cs. of normal hydrochloride acid, and adding water to 2,000 c.cs.
- or (b) Mixed bases given in gelatin capsules.
- or (c) Mixed bases given as a powder.

II.

Dosage.

For the first few cases of each series, a daily total of 20 grains.

For subsequent cases, a daily total either of one gramme, or of two grammes per 100 lbs. body weight (i.e. 0.022 g. or 0.044 g. per kilo).

For all cases, administered in two doses at approximately 10 a.m. and 4 p.m.

Type of case.

The cases treated are unselected, except that -

- (a) Cases unlikely to tolerate oral treatment.
- (b) Cases with a history of previous quinine treatment within three days of coming under observation.
- (c) Cases in any way complicated by other disease conditions.
- (d) A few cases of unusual severity are excluded.

All patients are of Indian, Chinese, Malay or Sikh nationality. They are of both sexes, of all ages from infancy to old age, and may be taken as fairly representative of the malaria admissions to a large district hospital serving the artisan, and peasant sections of the population.

Disappearance of Parasites.

Tables 1 and 2 contrast the efficiency of Totaquina in freeing the peripheral blood of parasites with that of quinine, only cases with no previous history of recent quinine treatment being selected for comparison.

TABLE 1.

		TOTAQUINA		QUININE	
RATE OF DISAPPEARANCE OF NON SEXUAL PARASITES FROM THE PERIPHERAL BLOOD AFTER COMMENCEMENT OF TREATMENT.				S.T. MALARIA 222 CASES.	
Within 1 day		9	per cent.	12	per cent.
" 2 days		27	" "	40	" "
" 3 "		33	" "	33	" "
" 4 "		14	" "	9	" "
" 5 "		9	" "	3	" "
" 6 "		5	" "	2	" "
" 7 "		2	" "	1	" "

TABLE 2.

		TOTAQUINA		QUININE	
RATE OF DISAPPEARANCE OF NON-SEXUAL PARASITES FROM PERIPHERAL BLOOD AFTER COMMENCEMENT OF TREATMENT.				B.T. MALARIA 78 CASES.	
Within 1 day		7	per cent.	9	per cent.
" 2 days		36	" "	43	" "
" 3 "		31	" "	36	" "
" 4 "		15	" "	9	" "
" 5 "		11	" "	3	" "
" 6 "		0	" "	0	" "
" 7 "		0	" "	0	" "

There is seen to be a slight lag in the disappearance of asexual parasites in the Totaquina treated series, when compared with the quinine series. This lag is rather more evident with subtertian than with benign tertian infections. It indicates a slight superiority of quinine over Totaquina, in so far as the rate of disappearance of parasites can be regarded as a criterion.

The quartan figures are too small for tabular comparison.

Duration of Fever.

Tables 3 and 4 illustrate the temperature response to treatment.

TABLE 3.

DURATION OF TEMPERATURE AFTER COMMENCEMENT OF TREATMENT.		S.T.MALARIA 222 CASES.
TEMPERATURE	TOTAQUINA	QUININE
1 Day	31 per cent.	37 per cent.
2 Days	32 " "	26 " "
3 "	9 " "	12 " "
4 "	8 " "	3 " "
5 "	2 " "	1 " "
6 "	0 " "	0 " "
7 "	0 " "	0 " "
Afebrile	17 " "	21 " "

TABLE 4.

DURATION OF TEMPERATURE AFTER COMMENCEMENT OF TREATMENT.		B.T.MALARIA 78 CASES.
TEMPERATURE	TOTAQUINA	QUININE
1 Day	45 per cent.	27 per cent.
2 Days	20 " "	34 " "
3 "	4 " "	9 " "
4 "	2 " "	3 " "
5 "	0 " "	0 " "
6 "	0 " "	0 " "
7 "	0 " "	0 " "
Afebrile	29 " "	27 " "

From these figures there appear to be no significant differences in the time of disappearance of fever in the Totaquina and quinine treated cases. In benign tertian malaria there is a trifling balance in favour of Totaquina.

Toxic Symptoms.

One of the objections sometimes raised against the use of cinchona febrifuge is its tendency to produce vomiting. Table 5 compares Totaquina with quinine in this respect. No significant difference is evident.

ANALYSIS OF TOXIC SYMPTOMS VOMITING		MALARIA; ALL TYPES 417 cases	
VOMITING PRESENT	TOTAQUINA	QUININE	
Before treatment	22 per cent	28 per cent.	
1st day	12 " "	12	" "
2nd "	22 " "	13	" "
3rd "	14 " "	17	" "
4th "	7 " "	10	" "
5th "	3 " "	6	" "
6th "	3 " "	3	" "
7th "	1 " "	1	" "

Dosage.

The doses used have usually been either 1 or 2 grammes daily for every 100 lbs. body weight. The former dose is not always high enough to be efficient, and the latter is occasionally not well tolerated. The optimum probably lies somewhere between the two, at round about 1.5 grammes, or 20 grains a day for the average Asiatic adult. For children a relatively larger amount is preferable and a daily dose of 2 grammes for every 100 lbs. is definitely more effective than 1 gramme, while being at the same time quite well tolerated.

Mode of Administration.

Totaquina can be given either in its original form as mixed bases, or in acid solution. On theoretical grounds the former is probably preferable. Capsules are convenient, but the powder can readily be given as such, washed down with a draft of water. This is a mode of administration which I would commend to the notice of those who have not given it a trial. The plain alkaloids, being much less soluble than their salts, are less bitter, while in acute malaria at least there seem to be sound theoretical reasons for limiting the intake of acid radicals.

If given in solution, the bihydrochloride and citrate solutions can be recommended. The bases are almost, but not completely, soluble in hydrochloric and citric acids, so the preliminary filtration is advisable.

The administration of Totaquina in a 50% solution of the bihydrochloride has been tried. The injections are decidedly more painful than are similar injections of quinine, and cannot be recommended.

CONCLUSIONS.

It is concluded that under the conditions prevailing in a large district hospital in the Federated Malay States, and on the type of malaria case admitted there-to, Totaquina gives excellent results. In a series of 417 cases, 236 were treated with Totaquina and 181 with quinine bihydrochloride in doses varying from somewhat above to somewhat below the customary clinical range. In therapeutic efficiency there was little to choose between the two drugs, such slight differences as were noted being in favour of quinine.

II. TOXICITY FOR ANIMALS.

Tests carried out by intravenous injections according to Giemsa's technique (C.H.Mal.183).

The toxicity for laboratory animals of Totaquina has been investigated. Table 6 summarises the findings. When administered intravenously to local rabbits in 1% solution no significant differences in the toxic effects of Totaquina and quinine are evident.

TABLE 6

DRUGS GIVEN INTRAVENOUSLY TO RABBITS IN ACID SOLUTION CONTAINING 1% OF BASE, A MINIMUM OF 5 MINUTES BEING TAKEN OVER EACH INJECTION				
DOSE IN GRAMMES PER 1 GRAMME BODY WEIGHT	TOTAQUINA II (Howard's)		QUININE	
	Survived	Died	Survived	Died
0.000019g.	4	0	4	0
0.000025g.	3	1	4	0
0.00003g.	4	0	2	2
0.000035g.	9	0	8	0
0.00004g.	1	1	2	1
0.000045g.	0	0	0	1
0.00005g.	0	1	0	0

The limit of tolerance for local rabbits was thus found to be 35 milligrammes per kilogramme; a total of 48 rabbits being used.

This figure is appreciably higher than that reported by Giemsa, who, using the same technique, found the maximum tolerated dose of a sample of Type II Totaquina which he submitted to test, to be 19 milligrammes per kilogramme.

(For this reason it was decided to repeat the tests on a small scale in order to confirm the local findings, and the following results have been communicated to the Secretariat by Dr. Field in a letter dated March 29, 1934).

Animal used	Body-weight in grammes	Drug	Dose per 1 gramme body-weight	Results
Rabbit 1	1,212	Totaquina	.000035 g.	Alive and well after 7 days
"	2	1,177	"	do.
"	3	1,042	"	do.
"	4	1,465	"	do.
"	5	1,020	"	do.
"	6	985	"	do.
"	7	1,220	Quinine	do.
"	8	1,110	"	do.
"	9	1,152	"	Died during inoculation
"	10	1,015	"	Alive and well after 7 days
"	11	1,014	"	do.
"	12	1,220	"	do.

The solutions (bihydrochloride) were of pH 3 to 3.5.

Though the repeated experiment was on a small scale only, the findings are in full agreement with those previously recorded.