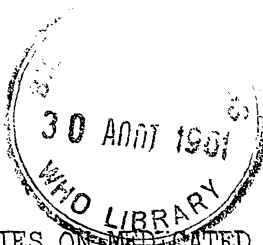


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WHO/Ma.1/299 ✓  
25 July 1961

ORIGINAL : ENGLISH

STUDIES ON MEDICATED SALT

Excretion of three chloroquine compounds

by

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1. Introduction

In a previous paper (Paulini, 1958) it was shown that medicated salt prepared with chloroquine diphosphate had unsatisfactory keeping qualities when stored under conditions of high relative humidity (more than 80%).

Later work (Paulini et al., in print) has shown that medicated salt of good keeping quality can be prepared using chloroquine compounds of low water solubility. It was, however, imperative to test the absorption of these compounds in man before any recommendation could be made for the substitution of chloroquine diphosphate. For the purpose of a comparative study of the intestinal absorption of various chloroquine salts, the assessment of urinary excretion was used, similar to that employed by Koenig & Fuhrmann (1956). It was postulated that if the absorption of a given chloroquine compound by the digestive tract was less complete than the absorption of chloroquine diphosphate, then the renal excretion of this compound would also be significantly less than that of chloroquine diphosphate.

The following products were used for this investigation:

Chloroquine diphosphate (62% base) - The drug, supplied by the Winthrop Sterling Institute (United States of America), was ground with pure NaCl in the proportion 1:2

Chloroquine naphthoate (45.2% base) (chloroquine methylene-bis- $\beta$ -oxynaphthoate) was supplied by the Farbenfabriken Bayer AG, Germany. The drug was ground and sieved (US Standard Sieve No. 200) and then thoroughly mixed with pure NaCl in the proportion 9.5:10.5

"Chloroquine adsorption compound" - was prepared as follows: 6 g of chloroquine diphosphate were dissolved in 60 ml of distilled water, then mixed with 18 g of magnesium silicate (Magnesol I.P.); the paste was dried in a water-bath, then finely ground and sieved.

The three types of compound were made up in gelatine capsules, each capsule containing the equivalent of 20 mg of chloroquine base.

Eight capsules were analysed from each group, giving the following content per capsule:

<u>Group</u>	<u>Salt</u>	<u>Chloroquine base (mg)</u> <u>mean content and S.E.</u>
A	diphosphate	19.8 ± 0.4
B	naphthoate	20.2 ± 0.4
C	"adsorption compound"	19.9 ± 0.2

## 2. Experimental technique

An experimental group of 12 persons consisted of 7-10 year old boys from the orphanage "Instituto Joao Pinheiro" of Belo Horizonte.

Since it was known from previous experience that there are considerable individual variations in the renal excretion of chloroquine, a rather large number of observations had to be collected in order to secure statistically significant results. The following scheme of drug administration was used:

Period	Individuals						Derivatives
	1-2	3-4	5-6	7-8	9-10	11-12	
I (21 days)	AA	BB	CC	AA	BB	CC	A= diphosphate
II (" " )	CC	AA	BB	BB	CC	AA	B= naphthoate
III (" " )	BB	CC	AA	CC	AA	BB	C= "adsorption compound"

Each period represented 21 days, and there was no interruption between periods. After completion of the three periods (63 days), the drug excretion was observed for eight additional days. All but one individual completed the whole course.

One capsule was given daily to each individual of the experimental group immediately after lunch, and was swallowed with a small amount of water.

A sample of urine voided in the morning, or forenoon, was taken for chemical analysis. The specific gravity of urine samples was determined immediately upon receipt at the laboratory. The samples were then stored in the refrigerator. The analysis of chloroquine was carried out using a double extraction method with "Amberlite IRC 50" ion-exchange resin. Details of this technique will be given in a separate publication. The chloroquine content of the acid extract was determined spectrophotometrically with a Beckman DU photometer. The chloroquine base concentration of the urine was recorded in mg per 100 ml (mg%). The drug concentration divided by the factor (Specific Density - 1000) x 100 has provided the "standard concentration" according to Yudkin as quoted by Bruce-Chwatt (1959).

The drug concentration of the daily urine samples was recorded in Graph 1. The daily variations were larger and in order to smooth out the curve a moving average of seven days was computed; it is shown as a dotted line on the graph.

### 3. Results

(a) From the data obtained the following general conclusions are evident:

No measurable quantity of chloroquine is excreted in the urine during the first few days of medication; this period was 3-5 days for "adsorption compound", 4-6 days for the diphosphate and 5-6 days for the naphthoate.

The excretion was more or less stabilized in the third (last) week of the first period; the excretion observed during that week was used for comparison purposes.

The urine became negative in 4-8 days after the last drug administration; there was no correlation between the compound used and the length of excretion after medication had been stopped.

(b) The daily excretions in mg% were totalled for each period (except in the first one, where only the last eight days were computed) and the mean daily concentration was calculated (Table 1).

The data obtained grouped according to the compound of chloroquine administered and according to the period of the test are shown in Table 2. These results show that:

There was no significant difference in the rate of excretion of the three compounds in the third week of the first period.

There was a definite increase of the excretion in the group taking the "adsorption compound" during the second period (fourth to seventh week) but not in the other two groups.

In the two groups taking "adsorption compound" and diphosphate, the mean excretion in the third period (eighth to eleventh week) was not significantly different from that in the first period, while excretion of the naphthoate was lower than in either of the two previous periods.

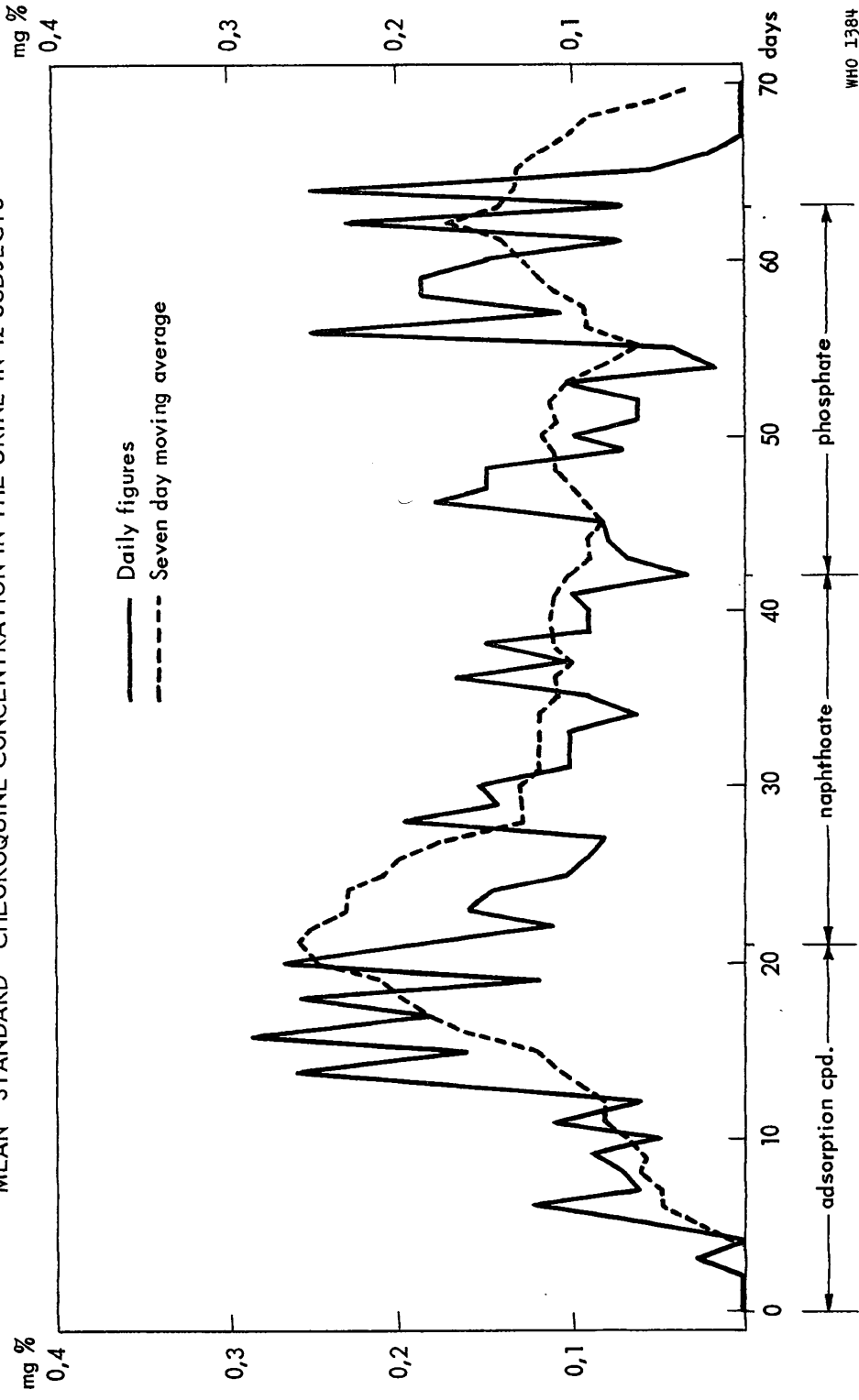
The mean excretion of the three compounds given in relative numbers and in decreasing order was:

	C	A	B
In the first period	10:	10:	10
In the second period	10:	8:	6
In the third period	10:	8:	6

for "adsorption compound", diphosphate and naphthoate respectively.

(c) Since it was found that there was a statistically significant difference in the individual mean excretions, an attempt was made to lessen this influence by expressing the relative excretion of the "adsorption compound" and of the naphthoate, taking the diphosphate excretion as standard. The relative values are shown in Table 3. Values greater than 1.0 indicate higher excretion and those less than 1.0 represent lower excretion than that of the diphosphate. It will be seen that out of the 12 values listed for naphthoate, eight are less than or equal to 1.0, whereas nine of 11 indices for "adsorption compound" are greater than or equal to 1.0. The median values are 0.85 for the relative excretion of naphthoate and 1.1 for that of "adsorption compound".

FIG. 1  
MEAN "STANDARD" CHLOROQUINE CONCENTRATION IN THE URINE IN 12 SUBJECTS





#### 4. Comments

It has been assumed in the introduction that the excretion of chloroquine taken orally in three different compounds will be in proportion to the rate of absorption of each. In fact, there is no direct evidence to prove this postulate; but knowing that:

- (a) both "chloroquine adsorption compound" and naphthoate decompose in media of low pH giving water soluble chloroquine salts;
- (b) all water soluble salts of chloroquine (sulfate, phosphate) are almost completely (80-85%) absorbed from the digestive tract (Koenig & Fuhrmann, 1956);
- (c) under normal conditions the amount of drug excreted in the urine is proportional to the amount of drug absorbed;

it seems reasonable to make such an assumption.

Therefore, the term excretion may be exchanged for absorption and, from the data presented in the previous chapter, it is concluded that the "chloroquine adsorption compound" is absorbed more readily by the human organism than the diphosphate, while chloroquine naphthoate is somewhat less well absorbed than the phosphate.

Chloroquine naphthoate was tested previously by various workers and considerable divergence in the results was observed. Koenig & Fuhrmann (1956) studied the renal excretion of this compound in comparison with that of other chloroquine salts; these workers found that the excretion of naphthoate was relatively little below the diphosphate excretion, the two being in a relative proportion of 9:10 (naphthoate: diphosphate).

Bruce-Chwatt & Charles (1957) found that naphthoate given orally to children in doses up to three times greater than chloroquine sulfate cleared malaria parasites from the blood of only 62% of the treated group; these results indicated that, comparing with chloroquine sulfate, less than 30% of the naphthoate was absorbed. Later, Charles observed (Bruce-Chwatt, personal information) that only 2.6% of the base was excreted in the urine after the oral administration of naphthoate, while the corresponding rate for chloroquine sulfate was 19%.

Clyde & Shute (1958) reported that a four times greater dose (calculated for base) of naphthoate was necessary to obtain results comparable with that of diphosphate, and suggested that absorption of the drug from the stomach may not be complete and hypochlorhydria may affect the results.

Koenig (personal information) suggested that the food taken concomitantly with naphthoate and specially the presence of sodium chloride might stimulate the secretion of stomach juice which in turn would increase the solubility of the naphthoate.

Our results suggest that the above consideration was sound since in most children in our experiment the naphthoate taken at meal times was nearly as well absorbed as the diphosphate.

Thus it seems that a small scale trial using chloroquine naphthoate in the form of medicated salt is justified. This compound has the advantage of not being subject to any significant amount of leaching.

#### SUMMARY

Three chloroquine compounds (diphosphate, naphthoate and chloroquine-magnesium silicate "adsorption compound") were given orally at meal times, during three periods of 21 days each, to 12 children of 7-10 years of age, in order to assess the absorption of the two practically insoluble chloroquine compounds (naphthoate and the "adsorption compound") in comparison with the diphosphate.

According to the relative renal excretion values obtained it was concluded that the "adsorption compound" was slightly better absorbed than the diphosphate, while the absorption of naphthoate was slightly lower.

Since the less soluble chloroquine compounds have very good keeping qualities in medicated salt, field trials with these products would be justified.

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TABLE 1. MEAN DAILY "STANDARD" CHLOROQUINE  
CONCENTRATION IN THE URINE OF 12 SUBJECTS.  
GIVEN THREE TYPES OF CHLOROQUINE SALTS

Subjects	Mean daily standard excretion of base in the three periods		
	First (last 8 days)	Second (21 days)	Third (21 days)
E.G.C.	A 0.24	C 0.25	B 0.16
G.C.	A 0.15	C 0.25	B 0.14
J.F.	B 0.09	A 0.15	C 0.13
F.E.A.	B 0.19	A 0.35	C 0.34
E.C.S.	C 0.22	B 0.14	A 0.11
E.C.G.	C 0.23	B 0.16	A 0.09
J.J.L.	A 0.20	B 0.21	C -
J.P.S.	A 0.12	B 0.14	C 0.14
O.S.J.	B 0.22	C 0.30	A 0.27
E.E.S.	B 0.21	C 0.26	A 0.19
O.M.	C 0.12	A 0.12	B 0.08
I.O.R.	C 0.17	A 0.19	B 0.08

A - Chloroquine diphosphate (range: 0.09-0.35 mg%)

B - Chloroquine naphthoate (range: 0.08-0.22 mg%)

C - Chloroquine "adsorption compound" (range: 0.12-0.34 mg%)

TABLE 2. MEAN DAILY STANDARD CONCENTRATION OF  
CHLOROQUINE BASE IN URINE DURING THREE CONSECUTIVE PERIODS

Chloroquine compound	Periods					
	First (last 8 days)		Second (21 days)		Third (21 days)	
	Individual means	Group mean + S.E.	Individual means	Group mean + S.E.	Individual means	Group mean + S.E.
"adsorption compound"	0.23 0.20 0.17 0.12	0.19 + 0.04	0.30 0.26 0.25 0.25	0.27 + 0.02	0.34 0.14 0.13	0.20 + 0.09
diphosphate	0.24 0.20 0.15 0.12	0.18 ± 0.05	0.35 0.19 0.15 0.12	0.20 + 0.09	0.27 0.19 0.11 0.09	0.17 + 0.07
naphthoate	0.22 0.21 0.19 0.09	0.18 ± 0.05	0.21 0.16 0.14 0.14	0.16 ± 0.03	0.16 0.14 0.08 0.08	0.12 ± 0.03

TABLE 3. "EXCRETION INDEX" OF CHLOROQUINE SALTS  
(DIPHOSPHATE TAKEN AS STANDARD)

Subjects	Compound 'A' taken in the period	C/A	B/A
E.G.C.	(1)	1.0	0.7
G.C.	(1)	1.7	0.9
J.J.L.	(1)	-	1.0
J.P.S.	(1)	1.2	1.2
J.F.	(2)	0.9	0.6
F.E.A.	(2)	1.0	0.5
O.M.	(2)	1.0	0.7
I.O.R.	(2)	0.9	0.4
E.O.S.	(3)	2.0	1.3
E.C.G.	(3)	2.5	1.8
O.S.J.	(3)	1.1	0.8
E.E.S.	(3)	1.4	1.1
Median value		1.1	0.85

A - diphosphate

B - naphthoate

C - "adsorption compound"