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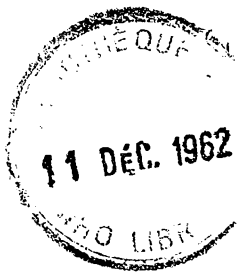

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COMPARATIVE STUDY OF THE CIRCULATION IN THE BLOOD AND ELIMINATION THROUGH THE URINE OF CHLOROQUINE ADMINISTERED IN THE FORM OF THE BASE OR SULFATE

by

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One of the principal difficulties in the Pinotti method (incorporation of chloroquine in household salt) is the "leaching effect" caused in the medicated salt by the ambient humidity so that part of the necessary concentration of the drug in the salt is lost.

Several methods for the overcoming of this disadvantage have been adopted - physical methods of protection such as air-tight packing, enveloping the medicament in a protective substance, etc.

At the Technical Meeting on the Chemotherapy of Malaria held by WHO in November 1960 in Geneva, we discussed the possibility of using an insoluble type of chloroquine, and it was proposed that the base be used since, being insoluble in water, it should not, a priori, be affected by the leaching effect.

Before making long-term storage experiments in a damp tropical environment with household salt to which chloroquine base has been added (experiments now proceeding), it seemed to us necessary to be certain of the therapeutic efficacy of the product, and we felt that the best way of confirming this would be to determine whether the administration of chloroquine base would, at the same doses, give the same blood levels as those achieved by the administration of a soluble salt.

In this work we compared the blood level and the urinary elimination after administration of a single dose of 600 mg (expressed in base) of either chloroquine sulfate or chloroquine base, and to this end we used two types of tablet, one containing chloroquine sulfate and the other chloroquine base.

The trials were carried out in Paris; they covered 10 adults, of whom five were given the base (600 mg in one dose) and five the sulfate (600 mg, expressed as base, in one dose).

(This experiment showed that in spite of its insolubility, chloroquine base was just as bitter as the sulfate.)

The chloroquine assay was carried out according to the Dubost & Allinne (1939) method, the principle of which is as follows:

After ether extraction of the base, the chloroquine sulfate is re-formed by shaking the ether with dilute sulfuric acid (1% by volume). Tanret reagent is added to the acid solution and the chloroquine assayed nephelometrically by comparison with a range of standard solutions of chloroquine in sulfuric acid (1 mcg-10 mcg).

In the tables set out hereunder we give details of the results obtained with respect to each of the treated persons; it will be seen that the blood concentrations of chloroquine are very similar in both cases: we found concentrations higher than, or equal to, 0.15 mg per litre up to the sixth or ninth day after administration of the sulfate, and up to the ninth day after administration of the base.

Urinary elimination was very similar in both cases. The figures for the fifteenth day after administration of the substance show the following results: chloroquine base - average elimination 23% (median 20.5%); sulfate - average elimination 20.5% (median 19%).

Taking individual variations into account, it will be seen that there was no appreciable difference between the two forms of the drug.

Similar tests to those reported here were made at our request at Bobo-Dioulasso by Captain Bentz (pharmacist). The results obtained in Africans (a smaller number: two given chloroquine base and two chloroquine sulfate) were identical with those obtained in Paris.

A few years ago, Fuhrmann & Koenig (1955) reported that when chloroquine was administered in the form of the free base there was less absorption than when it was administered in the form of sulfate or diphosphate. These authors found that 10 days after a single dose of 300 mg of chloroquine base, administered either in the form of the base or in the form of a salt, the cumulative percentage of chloroquine eliminated through the urine was 14.5% for the base, and 18.8% and 16.9% respectively for the diphosphate and sulfate.

We have not been able to confirm these findings of Fuhrmann & Koenig and although we are unable to explain this difference we feel that it may be useful to mention it.

REFERENCES

1. Dubost & Allinne (1939) Bull. Sciences pharmacol. 46, 367

2. Fuhrmann, G. & Koenig, K. (1955) Zeitsch. Tropenmed. & Parasit. 6, 431

TABLE 1. BLOOD CONCENTRATIONS OF CHLOROQUINE (MG/LITRE OF TOTAL BLOOD) AFTER ADMINISTRATION OF A SINGLE DOSE OF 600 MG OF CHLOROQUINE EITHER IN THE FORM OF THE BASE OR IN THE FORM OF THE SULFATE

Hours or days after administration of drug	600 mg of chloroquine base in the form of base					600 mg of chloroquine base in the form of sulfate				
	Subjects					Subjects				
	1 (Ntt.)	2 (Pak.)	3 (Ale.)	4 (Ehr.)	5 (Dem.)	6 (Pet.)	7 (Lef.)	8 (Bal.)	9 (Sch.)	10 (Saï.)
1 hour	1.60	2.5	1.33	0.15	1.0	2.25	0.75	0.75		
3 hours	1.25	2.25	1.0	1.25	1.0	1.50	0.50	0.75		
4 hours									1.2	0.50
5-6 hours	1.25	2.0		0.75	1.0	1.25	0.33	0.75		
24 hours	0.65	0.75				0.65	0.17		0.75	0.82
2 days	0.33	0.42	0.50	0.42	0.33	0.50	0.25	0.25	0.67	0.50
3 days		0.42					0.25		0.58	0.41
4 days	0.33				0.15	0.33		0.15	0.50	0.41
5 days			0.25	0.25						
6 days	0.33					0.15				
7 days	(outgoing patient)	0.25	0.25	0.17	0.33		0.15	0.15	0.33	0.33
8 days						<0.15				
9 days		0.25	0.15	0.15	0.25		0.15	<0.15	0.25	0.15
10 days										
11 days				<0.15				0	0.15	0.15
12 days										
13 days										
14 days			<0.15	<0.15	Traces			0		
15 days		<0.15					<0.15			
16 days								0		
17 days										
18 days										
19 days							Traces			

TABLE 2. URINARY ELIMINATION OF CHLOROQUINE (MG PER 24 HOURS) AFTER ADMINISTRATION OF A SINGLE DOSE OF 600 MG OF CHLOROQUINE EITHER IN THE FORM OF THE BASE OR IN THE FORM OF SULFATE

Hours or days after administration of drug	600 mg of chloroquine base in the form of base					600 mg of chloroquine base in the form of sulfate				
	Subjects					Subjects				
	1 (Ntt.)	2 (Pak.)	3 (Ale.)	4 (Ehr.)	5 (Dem.)	6 (Pet.)	7 (Lef.)	8 (Bal.)	9 (Sch.)	10 (Saï.)
24 hours	69	55	37.5	27.0	17.5	40.0	14.0	22.0	42.0	83.0
2 days	33	30	16.0	22.5	7.5	15.0	8.5	15.0	14.5	42.0
3 days	26	18.7	9.1	12.0	14.5	11.25	9.0	6.2	7.5	20.4
4 days	12.5	15	6.25	7.5	22.5	7.5	3.8	4.4	11.3	16.8
5 days	12.5	17.5	4.15	9.0	12.5	8.8	7.0	6.5	7.5	20.0
6 days	11.6	7.5	8.8	8.8	8.7	10.0	5.4	6.0	3.6	11.0
7 days	11.6	9.4	2.5	4.8	8.3	6.7	3.6	3.3	3.6	7.0
8 days	(outgoing patient)	6.3	5.6	7.8	4.5	5.0	5.4	2.75	3.6	5.5
9 days		9.0	9.2	6.0	4.15	5.3	1.0	2.5	4.0	7.5
10 days		5.0	3.35	4.8	4.0	5.3	4.9	3.2	2.5	4.8
11 days		3.5	2.7	4.6	4.95	5.0	7.5	2.9	3.1	5.2
12 days		4.1	0.9	1.1	3.8	4.0	3.0	2.7	3.7	
13 days		3.75	3.2	2.3	4.3	6.7	3.75	2.8	3.0	0.75
14 days		3.35	2.35	4.4	4.1	4.1	2.0	2.4	2.0	2.5
15 days		3.35	3.1		3.8	3.5	1.6	3.5	3.0	4.5
16 days		3.35	4.0	3.25	4.0	5.8	1.85	1.4		3.5
17 days		2.0	1.65	2.9	3.15	7.0	5.0	1.75		4.0
18 days		1.8	3.15	3.35	2.35	3.0	2.0	2.25		2.75
19 days		1.35	3.3	3.05	3.3	2.5	3.5			
20 days		2.15	2.75		2.2		2.0			
21 days					2.3					
22 days			2.45		2.0					
23 days			2.15		2.4					
24 days			2.0		5.6					
25 days			2.0							

TABLE 3. CUMULATIVE PERCENTAGE OF CHLOROQUINE ELIMINATED THROUGH THE URINE AFTER ADMINISTRATION OF A SINGLE DOSE OF 600 MG OF CHLOROQUINE BASE EITHER IN THE FORM OF THE BASE OR IN THE FORM OF SULFATE

Hours or days after administration of drug	600 mg of chloroquine base in the form of base					600 mg of chloroquine base in the form of sulfate				
	Subjects					Subjects				
	1 (Ntt.)	2 (Pak.)	3 (Ale.)	4 (Ehr.)	5 (Dem.)	6 (Pet.)	7 (Lef.)	8 (Bal.)	9 (Sch.)	10 (Saï.)
24 hours	11.5%	9.1%	6.2%	4.5%	2.9%	6.6%	2.3%	3.6%	7.0%	13.8%
2 days	17.0	14.0	8.9	8.2	4.0	9.1	3.75	6.0	9.4	20.6
3 days	21.3	17.2	10.4	10.2	6.5	11.0	5.2	7.2	10.6	24.0
4 days	23.4	19.7	11.4	11.5	10.0	12.25	5.8	7.9	12.5	26.8
5 days	25.5	22.7	12.1	13.0	12.4	13.75	7.0	9.0	13.7	30.2
6 days	27.4	23.9	13.6	14.4	13.8	15.4	7.9	10.0	14.4	32.0
7 days	29.3	25.5	14.0	15.2	15.2	16.5	8.5	10.5	15.0	33.2
8 days	(outgoing patient)	26.5	14.9	16.5	16.0	17.3	9.4	11.0	15.6	34.1
9 days		28.0	16.5	17.5	16.6	18.2	9.6	11.4	16.2	35.3
10 days		28.9	17.0	18.3	17.3	19.1	10.4	11.9	16.6	36.1
11 days		29.4	17.5	19.1	18.1	19.9	11.6	12.4	17.2	37.0
12 days		30.0	17.6	19.3	18.8	20.6	12.1	12.9	17.8	
13 days		30.79	18.2	19.5	19.5	21.7	12.8	13.3	18.3	37.1
14 days		31.3	18.6	20.2	20.2	22.4	13.1	13.7	18.6	37.6
15 days		31.9	19.1		20.8	23.0	13.4	14.3	19.1	38.3
16 days		32.4	19.7	20.7	21.5	23.9	13.7	14.5		38.9
17 days		32.8	20.0	21.2	22.0	25.1	14.5	14.8		39.5
18 days		33.1	20.5	21.7	22.4	25.6	14.8	15.0		40.0
19 days		33.3	21.1	22.2	22.9	26.0	15.4			
20 days		33.6	21.5		23.3		15.8			
21 days					23.7					
22 days			22.0		24.6					
23 days			22.3		24.4					
24 days			22.6		25.4					
25 days			23.0							

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