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DE LA SANTÉ

EXPERT COMMITTEE ON MALARIA

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ENGLISH ONLY*

The Secretary of the Expert Committee on Malaria has the honour to communicate hereunder a

SUMMARY REVIEW OF LITERATURE ON

C A M O Q U I N

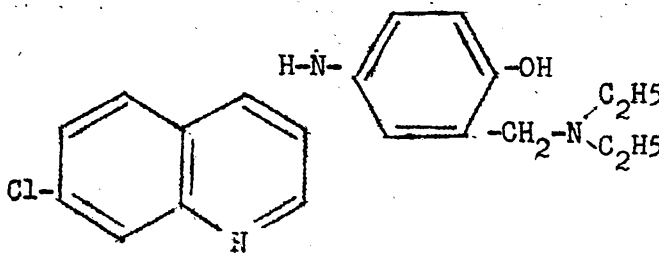
prepared by the Malaria Section

Camoquin** was synthesized during World War II by the PARKE & DAVIS, CO. Ltd. Research Laboratories of DETROIT (Michigan), USA, and was first reported at the meeting of the American Chemical Society in 1946.⁽³⁾

Chemical make-up and chemico-physical characteristics:

Camoquin is a 4-aminoquinoline derivative with the chemical name of: 4-(3' diethylaminoethyl, 4'hydroxyanilino)-7-chloroquinoline, or 4-(7-chloro-4-quinolylamino)- α -diethylamino-o-cresol, the developed formula of which is :

→ formula



* For reasons of economy, no translation made in French.

** Synonyms: CAM-AQI, Miaquin, SN.10.751, Amodiaquin.

A significant difference of this drug when compared with chloroquine and sontoquine, which are also 4-aminoquinolines, is the presence in the side-chain, in the 4-position, of an amino-o-cresol.

It is generally prepared as the dihydrochloride dihydrate, and under this form it is a yellow crystalline powder of which 1 g. dissolves in 5 cc of water at 25°C. (9)

Form of Supply

The drug, formerly supplied under the form of tablets containing 0.05 of the base (the actual amount of the salt being 0.065gm⁽¹⁴⁾) is at present supplied as grooved tablets each representing 0.2 gm of camoquin base.

Laboratory investigations:

Experiments conducted with laboratory animals have shown that Camoquin is rapidly absorbable from the gastro-intestinal tract. It is unequally distributed in the body tissues, as is evident in the following table, which gives also the distribution of chloroquine and of quinacrine (mepacrine).

Table I

Distribution of camoquin, chloroquine and quinacrine in the Tissues of the Monkey (2)			
Tissue or Organ	Mg Drug per Kg Tissue		
	SN 7,618 (chloroquine)	SN 10,751 (camoquin)	Quinacrine
Plasma	3.62	0.41	0.19
Brain	48	31	7.8
Heart	265	59	258
Lung	298	87	940
Liver	776	550	1450
Spleen	195	119	475
Kidney	208	60	161

All the monkeys received the same daily dose of the drug (25 mg base per kg body weight) for a period of 30 or 31 days. All were killed at approximately the same time after receiving the last dose of drug. The concentrations of the 4-aminoquinolines were determined by means of a modification of the dye method of Brodie. Quinacrine was determined by Brodie's double-extraction procedure.

Camoquin is present in higher concentrations in the tissues and in the erythrocytes than in the blood plasma, where it can, however, reach a high level.

Table II

Plasma levels (micrograms per litre) of Camoquin, in dogs and monkeys, after a single dose of drug (50 mg/kg orally in aqueous solution)⁽²²⁾

<u>Hours after dose</u>	<u>Dog</u>		<u>Monkey</u>	
	<u>Plasma</u>	<u>Erythrocytes</u>	<u>Plasma</u>	<u>Erythrocytes</u>
1:00	665	860		
2:00			620	226
3:00	215	914		
4:00			295	273
5:00	195	290		
6:00			320	580
7:00	114	282		
24:00	39		41	135
48:00			29	13

It has with the other 4-aminoquinolines the advantage of causing very little or no staining of skin tissues.⁽⁸⁾ It can be found in the white cells of the blood twenty-three days after administration⁽²²⁾.

The drug is extensively degraded in the animal body, less than 1 percent of a single oral dose being excreted in the urine of dogs during the first 24 hours after dosage; like mepacrine, it is slowly excreted from the body on cessation of administration.⁽⁴⁾

In human subjects, experiments made by R. W. BERLINER & al. in 1947,⁽¹⁰⁾ demonstrate that the drug concentration of Camoquin is bound to non-diffusible constituents of the plasma to as great a degree as quinacrine. "The degradation products are chemotherapeutically active and are slowly eliminated, plasma concentrations declining at the rate of about 60 percent per week."⁽²⁾

Table III

Relationship in human beings between plasma drug concentration and various daily oral doses of: chloroquine (SN 7618), sontoquine (SN 6911) and camoquin (SN 10,751)⁽¹⁰⁾

<u>D r u g</u>	Daily dosage (mg)			
	50	100	200	300
	<u>Mean plasma drug concentration μ/L</u>			
Sontochin			107	179
Chloroquine	22	49	110	176
Camoquin	3.6	9.3	19	34

N.B. Figures for Camoquin include an unknown fraction of degradation product.

TOXICITY

Acute toxicity: The acute toxicities of Camoquin and quinacrine are roughly the same in rats and mice. In dogs, i.v. infusion of 8-15 mg/kg at rates of 15-30 mg/kg/hr., bigeminal cardiac rhythm developed, and ventricular fibrillation was noted in one animal out of five. There was no evidence of negative inotropic effect on the myocardium. Death usually resulted from respiratory paralysis.⁽⁴⁾

Chronic toxicity: In the dog, a daily dosage of quinacrine in excess of about 10 mg/kg daily is accompanied by vomiting or diarrhoea; up to 40 mg/kg/day of Camoquin is tolerated before these symptoms become manifest.

The monkey likewise tolerates 25-40 mg/kg/day of Camoquin without undue weight loss or gastro-intestinal symptoms.

In rats, 150 mg/kg/day of quinacrine is fatal in 5-8 days; 60 mg/kg/day is fatal in 2-4 weeks, and 30 mg/kg/day is fatal in 6-12 weeks (Siegel and Muskett: Arch.Path.,38,63,1944). A 0.2 percent diet of Camoquin, supplying about 200-300 mg/kg/day, is fatal to rats in 6-12 weeks.⁽⁴⁾

The pathological picture of repeated dosage of the drug in dogs and monkeys resembles that of quinacrine, i.e., lipoidosis of the reticulo-endothelial cells, of the liver and spleen, and cloudy swelling and fatty degeneration of the tubular

epithelium. In rats it causes necrosis of the liver. (8)

Tests made with white chicks showed that the "maximum tolerated" dose of Camoquin is equivalent to 1/5 that of quinine*.

In the mouse, the criteria for toxicity being loss of weight and death, it has been seen that Camoquin is four times less toxic than quinine (2), and in the rat the toxic amount of Camoquin is 1/5 that of quinine. (2)

ACTIVITY

The great majority of tests on activity have been made in birds (turkeys, chicks and canaries), dogs and monkeys.

Camoquin is several times as effective as quinine and quinacrine. (4) (12)

As a therapeutic, in the duck, against blood-induced Plasmodium lophurae and cathemerium infections, the minimum effective dose by mouth to produce a decrease in the number of parasitized red cells, is respectively 1/15 and 1/30 that of quinine. Mepacrine would be respectively 1/4 and 1/1.8. (2) (1.d)

Suppressive tests

(We remind that, according to WISELOGLE, a drug showing suppressive activity will cause a decrease in the extent of the parasitaemia relative to that of control birds which have not received the drug.)

a. Blood-induced gallinaceum infection in the chick:

one dose of Camoquin will produce the same lowering of parasitaemia as eight doses of quinine. As quinine is effective in doses of 32 mg daily, the equivalent dose of Camoquin will be 32/8, i.e., 4 mg. (1.d) (2)

b. Blood-induced gallinaceum malaria in the chick:

the minimum detectable reduction of parasitaemia would be obtained with 16 mg/kg daily of quinine and 16 mg/30/kg daily of Camoquin.

Using the quinine dihydrochloride monohydrate, one dose of Camoquin would produce the same effect as 20 doses of quinine salt. (2)

* The "maximum tolerated dose" is the greatest amount which birds survive with a final weight (on the morning after the last dose) at least equal to the starting weight (on the morning before the first dose.)

Camoquin as a Suppressive (2)

Animal	Blood-induced malaria with:	Minimum effective dose suppressing malaria symptoms in quinine equivalent*
Canary	<u>P. cathemerium</u>	1
Chick	<u>P. gallinaceum</u>	8
Chick	<u>P. lophurae</u>	30
Canary	<u>P. cathemerium</u>	6

Three sub-strains of P. lophurae exposed to Camoquin and chloroquin for approximately 200 days (under conditions similar to those used in inducing resistance to proguanil) indicate that this parasite is unable to become adapted readily to either of these drugs. (11)

Prophylactic tests:

a. Sporozoite-induced gallinaceum malaria in the chick:

1. (Protection test): the maximum tolerated dose of Camoquin has no preventive action. It is equivalent to 1/2 the minimum preventive dose of sulfadiazine (that is the dose which prevents the appearance of parasites in at least 50 percent of the birds of a series, throughout 35 days of observation (WISELOGLE)).

2. (Delay test): (The minimum delaying dose of a drug is the lowest dosage that delays the appearance of parasites in at least half of the birds of a test group for 4 or more days beyond the day on which more than half of the controls have shown parasites. According to WISELOGLE, this effect is usually produced by 31.2 mg/kg daily of sulfadiazine. The sulfadiazine equivalent is determined by dividing the minimum delaying dose of sulfadiazine by the minimum delaying dose of the test drug.)

In the same conditions, the maximum tolerated dose of Camoquin (103.9 mg/kg/day) produces no delay in the appearance of parasites. (2)

b. Sporozoite-induced lophurae malaria in the turkey

Camoquin is inactive. A dose of 60 mg/kg daily gives no prolongation of the prepatent period. (2)

* According to WISELOGLE the quinine equivalent is the ratio by weight of the dose of quinine to the dose of the drug under assay when both drugs, administered under identical conditions, produce the same response in parasitized birds. (2)

- c. Sporozoite-induced cathemerium malaria in the canary: Camoquin is unable to prevent the appearance of parasites. The incubation period at 580 mg/kg daily was 5.0 days , - Controls: 4.7 days. (2)

USE OF CAMOQUIN IN HUMAN MALARIA

Since the drug has been synthesized it has been used on a rather limited scale against the different types of human malaria. "Its antimalarial activity appears to be analogous to that of chloroquine" (2) (9) (12) (23).

In most cases it is administered orally, and seems to be as effective as when administered by intra-muscular injection. (24) (21)

Nine subjects with blood-induced falciparum malaria (McClendon strain) received total dosages varying from 0.375 to 0.8 g. Four of them resulted in temporary suppression of parasitaemia and/or fever, and five in "permanent" effect, i.e , absence of parasitaemia for 14 days (vivax) and 21 days (falciparum) (followed by a positive reinoculation to indicate continued host susceptibility to the infection.) (10) (1.c)

The experiments so far made demonstrate that it is probably equally effective against the asexual forms of all types of malaria parasites. (14) But, whereas it proves active against the gametocytes of vivax, it is of little or no value against the gametocytes of falciparum parasites. Nonetheless, Sister M. Mercy reported that Camoquin hydrochloride cleared the blood of gametocytes in resistant P.falciparum infections when the dosage was increased to a total of 3 to 5g_m given over two and three days respectively. (9)

Since the preliminary studies of SIMMONS and CHHATRE (9) who established that a dose of 10 mg/kg body weight was the minimum effective dose which would produce satisfactory results, most authors have started on that base. The total dosage generally administered is therefore included within limits of 0.4 and 0.6 g in the adults. But in Bolivia and Southern Brazil, 0.8 to 1 g Camoquin are frequently given as a single dose. The lower doses do not give as good results for controlling the clinical attacks. (9) (16)

Concerning the regime of administration, the best results are reached with the single dose schedule (14) (19) which terminates the acute attacks earlier than the other schedules, gives a lower relapse rate and is easier to control and

administer, particularly in rural areas.

In India, SIMEONS and CHHATRE⁽⁹⁾ observed that a dose of 10 mg/kg body weight administered to 116 inmates of a school (in a malarious area), where during the preceding months there had been a considerable loss of attendance due to malaria, prevented the appearance of any malaria case during the following two months.

Table IV summarizes available reports on camoquin in human malaria.

Relapses:

Referring to the experience so far reached with Camoquin, it seems that it will delay attacks for at least 2 to 3 months in the majority of cases of all types of infection.^{(8) (9) (27)} Relapses of vivax malaria are delayed almost as long as after chloroquine ^[(23) quoted by COOPER.⁽¹⁹⁾] But this particular point requires a more accurate study.

Toxicity:

In the observations made by most of the authors, Camoquin gave no toxic reactions. When some symptoms were observed, these consisted of: nausea, vomiting, diarrhoea, headache, tenesmus, palpitation, fainting, but in no case were there any after effects. (A man received 1gm in 24 hours without sign of toxicity). In the experience of CHAUDHURI & al. the single dose of 10 tablets, i.e. 0.5gm of the base was well tolerated and this amounted in some underweight subjects of the younger age to as much as 20 mg/kg/body weight, which is the doubt of the optimum dose fixed by SIMEONS AND CHHATRE. Not even with pregnant women and patients with cirrhosis of the liver was the drug toxic. (MEIN, R.)

With high dosages (of from 50, 100, 200, 300 up to 400 mg. daily over a period of five weeks) some people had symptoms sufficiently severe to make it necessary to stop working.^{(10) (L.f)}

It seems that we may now conclude that Camoquin is a good suppressant and an excellent schizonticide, the "most powerful with chloroquine"⁽²¹⁾. A single dose treatment of 0.5 to 0.6gm will prove effective especially for semi-immune populations. Camoquin does not sterilize crescents, but it can be used effectively in falciparum infections, either alone or as a reinforcement of a proguanil treatment. It may also be employed, like chloroquine or proguanil (100 mg in each case) when the treatment is over, as a weekly maintenance dose for six weeks⁽²¹⁾ "to cover the period when recrudescences are likely to occur."

P.S. Camoquin is at present supplied under the form of tablets, each containing 0.20 gm. 4(3'-diethylamino-methyl-4'-hydroxyaniline)-7-chloroquinoline, as the dihydrochloride dihydrate.

The recommended dosage is : Adult, 3 tablets (0.60 gm) to be taken as a single dose;
Children from 5 to 15 years of age: 2 tablets (0.40 gm.);
Under 5 years of age : 1 tablet (0.20 gm);
or as directed by the physician.

TABLE IV

Summary of reports on Gamouquin in human malaria

* Authors and Reference	Number of cases			Total dosage in grams of the base and Regime:	Time for fever to subside	Time for asexual parasites to disappear			
	Falc.	Vivax	P + V. Quart.			Falc.	Vivax	Falc.+Vivax	Quart.
Halawani, A.-Bez, I.- Morcos, P. (8) Egypt (J. Roy. Egypt. Med. Ass., 30; 2; Feb. 1947; 99-103)	1	29		Divided dose (a.d.): 0.45 in 4 days 0.40 in 2 days 0.50 in 2 days 0.40 in 1 day	1 - 2 days	1 day	1-2 days, 5 days in many cases		
Simeons, A. T. W.-Chhatre, K. D. (Ind. Med. Gaz., 87; 5; May 1947; 255-257) India	11	39		Single dose (s.d.): 0.4 to 0.8 (Infants up to 2 years : 0.1 g. Children from 2-5 years : 0.2 " " 5-14 years: 0.3 Average (light adults) : 0.4 " (heavy adults) : 0.6-0.8	27 - 28 hrs Maximum : 48 hrs	25 hrs Range: Few hrs to 40	23 hrs Range: Few hrs to 46		
Mein, R.M. (13) (Proc. 4th Intern. Congr. Med. & Mal., Washington '48 773-774) (Rev. Serv. Spec. Sante Publ. Inde, 1948; 1059-1069. Brazill)	21	64	2	Single dose: 0.5) adults 0.4) 0.25) children 0.1-0.2)	30 hrs	48 hrs	48 hrs	48-72 hrs	
Chaudhuri, R.W. (12) (Ind. Med. Gaz., May, 1948; 225-230) India			3	Single dose: 0.5 Divided dose: 0.6 in 3 days	2d day in 85% of cases			2 days for asex.falc. 1 day for asex.vivax	1 day for asex.forms 2 days for sex.forms
Chaudhuri, R.W.-Chakravarty N.K. (14) (Ind. J. Malariol., 2; 3; Sept. 1948; 115-127) India	23	23	3	Single dose: 0.5 Divided dose: Below 4 years: 0.15 in 3 days From 4 to 8 y.: 0.3 " " From 8 to 12 y.: 0.45 " " Above 12 years: 0.6 " "	2d day in 85% of cases 3d day in 14% " " Average duration with divided dose: 30 hrs. Average duration with single dose: 22 hrs.	24 hrs	24 hrs	24 hrs	24 hrs
Ejerito, A.-Duque, M. (15) (Phil. Med. Ass. J., Manila, 24; Nov. 1948; 633) Philippines	22 prim 22 rel.	40 prim 44 rel.		Single dose: 0.4	3 days 5 days in prim. Falc. cases Range: 1 to 5 days	3 days (rel.) 5 days (prim.) febrile	3 days (rel.) 1-2 days in prim. afebr. 3-4 days in prim. febrile		

TABLE IV
Summary of reports on Camoquin in human malaria

Action on Gametocytes	Relapses	Toxicity
Nil	Out of 30 cases followed up for 3 to 5 months : no relapse.	During the treatment, nausea, vomiting, diarrhoea, tenesmus, headache, palpitation, fainting. - But one man received up to 1g./24 h. without sign of toxicity. - No lasting effects.
Nil	No relapse after 3 months.	Nil
30% of failures with falciparum gametocytes	Some cases remained negatives 18 months after. But the area was highly endemic, it was therefore difficult to control.	Nil, even to pregnant women and patients with cirrhosis of the liver.
Negative for falc after 5 days " " vivax after 3 days		Nil
Crescents were seen up to 26 days Average duration. 7.8 days Range: 1 to 26 days. In quartan and vivax infections, gametocytes disappeared within 1-5 days (from the day the drug was administered)	1 falciparum: 20 days after infection. 2 mixed (F+V): 40 and 60 days after respectively. Out of 45 cases followed up for 1 to 8 months: 17 relapses. (It is not certain that all the cases were relapses or reinfections)	Nil, even with 20 mg/kg body weight.
Negative after 4-9 days in prim. falciparum Commence to disappear after 19 days in relapse falciparum.	10 relapses (7.8%) within 12 months, i.e.: 2 prim. vivax (39 and 56 days after resp.) 7 relapse vivax (Range 31 - 34 days) 1 relapse falciparum (81 days later)	Nil

* Authors and Reference	Number of Cases				Fetal dosage in grams of the base and Regime:	Time for fever to subside	Time for asexual parasites to disappear			
	Falc.	Vivax	F + V	Quart.			Falc.	Vivax	Falc.+Vivax	Quart.
Patel, J. C.-Mehta, J.M. (16) (Ind. J. Med. Sci., 2: II; Nov. 1948; 675-679) <u>India</u>	9	22	5		Single dose: 0.25 Divided dose: 0.25 in 48 hrs	Vivax 26.5 hrs(s.d) 49.8 hrs(d.d) 47.3 Range: 24-60 hrs(s.d) 24-96 hrs(d.d)	63.7 hrs	60.0 hrs 59.7 "	61.6 hrs 62.5 "	
Halawant, A.-Baz, T.-Morkos, F. (Ann. Trop. Med. & Parasitol. Dec. 1948; 304-311) <u>Egypt</u>	3	85			Divided dose: 0.5 in 1 day	1 day	1 day Range: 1 to 4 days	1 day		
Doane, L.M. (18) (Proc. 4th Intern. Congr. Trop. Med. & Mal., Washington, 1948; 769) <u>Brazil</u>	42	88		2	Single dose: 0.5	2 days	2 days	1-3 days		3 and 4 days resp.
Hoekenga, M.F. (27) (quoted in 26.) <u>Panama</u>	20	30			Single dose: 10 mg./kg.	48 hrs.	30 hrs	37 hrs		

Action on Gametocytes	Relapses	Toxicity
<p>No effect at all on 7 patients</p>	<p>Out of 20 patients followed up for 4 months: 1 falciparum: 11 days after 4 vivax : after an average of 40 days Range: 30 to 49 days)</p>	<p>Nil</p>
<p>Negative for 2 falcip. after respectively 4 and 8 days. Out of 15 vivax: 5¹/₄ negat. 2⁸/₄ day 3¹/₄ " 5¹/₄ day 4 " 4¹/₄ day after treatment</p>	<p>4 relapses within 6 months</p>	<p>In a few cases: severe headache for 2 days, nausea, vomiting, abdominal colic, diarrhoea. No ill effects after cessation of treatment</p>
<p>Out of 34 falcip. with gametocytes 27 remained positive after 7 days. In 4 falcip. cases followed up: gametocytes persisted many days; in one case, 31 days after treatment. Out of 77 vivax with gametocytes, all were negative after 7 days.</p>	<p>One vivax relapse (follow up: 6-16 months)</p>	<p>Nil</p>

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