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Research Article

STUDIES ON THE CHEMOTHERAPY OF THE HUMAN MALARIAS. VI. THE PHYSIOLOGICAL DISPOSITION, ANTIMALARIAL ACTIVITY, AND TOXICITY OF SEVERAL DERIVATIVES OF 4-AMINOQUINOLINE [1, 2]

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One of the major contributions of the wartime malaria research program was the development of a number of synthetic antimalarial drugs with suppressive activity superior to that of quinacrine. Of the various chemical compounds examined, certain derivatives of 4-aminoquinoline are among the more promising.

The 4-aminoquinolines had been considered as potentially useful antimalarial agents prior to the war and, in fact, a number appear in the patent literature. Translated abstracts of the Russian literature deal with several members of this series (1). However, there is little evidence that these compounds had received adequate pharmacological, toxicological, or clinical study. One 4-aminoquinoline, SN–6911 (santochin), had been studied early in the course of the systematic survey of antimalarials in this country and had shown high activity in gallinaceum malaria in the chick (2, 3). However, the lead suggested by this observation was not appreciated at the time.

It was not until the French found SN–6911 to be well tolerated and to have high activity in the human malarias that a serious effort was made, in this country, to explore the 4-aminoquinoline series. A short time before, Blanchard had expressed interest in the potentialities of these compounds (4). A consideration of the chemical structure of quinacrine and related compounds led him to believe that derivatives of less complex nuclei should possess high antimalarial activity. He viewed the relationship of two such chemical series to quinacrine as shown in Figure 1.

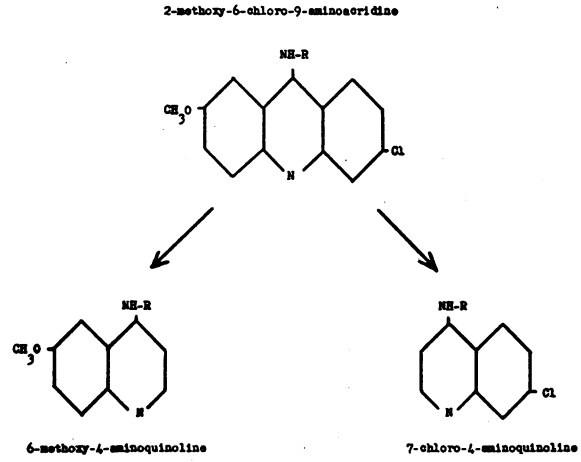

FIG. 1. RELATIONSHIP TO QUINACRINE OF TWO 4-AMINOQUINOLINE SERIES

A large number of derivatives of 4-aminoquinoline have since been synthesized. These were examined for antimalarial activity in avian malarias and the most active were subjected to mammalian toxicity studies. The ten compounds shown in Table I have received trial in the human. It is the purpose of the present communication to report on studies of the physiological disposition, antimalarial activity and toxicity of several of these compounds.

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[3] Captain, MC, AUS.

TABLE I

Structure of the substituted 4-aminoquinolines studied

The antimalarial activity of SN-7373 and SN-10,960 was studied by the Boston group (5)

Survey number	Nuclear substituents	Substituent on 4-amino group
SN-3294	6-methoxy	diethylamino-1-methyl butyl
SN-6911	3-methyl-7-chloro	diethylamino-1-methyl butyl
SN-7135	2-methyl-7-chloro	diethylamino-1-methyl butyl
SN-7618	7-chloro	dethylamino-1-methyl butyl
SN-8137	7-chloro	diethylamino-2-hydroxy propyl
SN-9584	7-chloro	diethylamino propyl
SN-10,751	7-chloro	α-diethylamino-o-cresol
SN-13,425	7-chloro	1′-ethyl-4′-piperidyl
SN-10,960	7-chloro	diethylamino-3-hydroxy butyl
SN-7373	7-bromo	diethylamino-1-methyl butyl

CHEMICAL

The procedure developed for the estimation of each of the 4-aminoquinolines in biological materials involved the use of one of three general reactions.

1. The conversion of a non-fluorescent 4-aminoquinoline to a highly fluorescent substance by irradiation with near ultraviolet light (6). This is accomplished by irradiation of the compounds in an aqueous solution at pH 9.5 in the presence of cysteine to prevent further oxidation of the fluorophore formed. Several of the 4-aminoquinolines appear to yield the same fluorophore, since all of the compounds estimated with this procedure have the same relationship between quinoline concentration and intensity of fluorescence. This method was used for the estimation of SN-7618, 8137, 10,751, 7135, 13,425.

2. The formation of an organic-soluble, water-insoluble complex of the 4-aminoquinoline with methyl orange (7). This procedure was used for the estimation of SN-6911 only. The conversion of SN-6911 to a fluorophore requires radiant energy of a lower wavelength than was readily available. However, the rather high plasma drug concentrations obtained permitted the use of the less sensitive methyl orange reaction.

3. The direct measurement of fluorescence in an organic solvent (8). This method was used for the estimation of SN-3294 since the compound itself is highly fluorescent.

The evidence available indicated that the methods used for estimating the concentrations of the 4-aminoquinolines in biological materials are reliable and, in general, highly specific. The SN-3294 and SN-10,751 methods are exceptions in that certain metabolic products of the drugs are included in the final determination.

Section I

PHYSIOLOGICAL DISPOSITION

The data presented in this section describe some of the important aspects of the physiological disposition of the 4-aminoquinolines. Each compound was studied to obtain information relative to absorption from the gastro-intestinal tract, renal excretion, distribution in various tissues, binding on the non-diffusible constituents of plasma, and the effect of these discrete processes in determining the relationship between oral dosage and plasma drug concentration.

TABLE II

Absorption and excretion of several 4-aminoquinolines

Drug	Number of patients	Daily dose	Mean plasma concentration	Excretion			
				Stool		Urine	
		grams	*μg./L*	*mg./24 hrs.*	*percentage of daily dose*	*mg./24 hrs.*	*percentage of daily dose*
SN-3294	2	0.4	560	15	4	88	22
SN-6911	3	0.6	449	15	3	140	23
SN-7135	2	0.3	197	22	7	62	21
SN-7618	2	0.4	217	31	8	57	14
SN-8137	2	0.3	181	4	1	40	13

Absorption and excretion were examined in balance studies in which the subjects received a soluble salt of a drug over a period of days until plasma drug concentrations had become stable. Urine and stool collections were made during the last 48-hour period of drug administration (Table II). The small amount of drug recovered from the stools in each instance indicates fairly complete absorption from the gastro-intestinal tract. At equilibrium the urinary excretion, under ordinary conditions, accounts for 10 to 25 per cent of the daily oral dose. However, the rate of renal excretion can be made to vary over a wide range by the concurrent administration of acid or alkali, being increased by acid and decreased by alkali. Detailed studies relating acid-base balance and the physiological disposition of the 4-aminoquinolines are reported in a separate communication (9).

Data on the distribution of two compounds (SN–3294 and SN–7618) in the body fluids and

TABLE III

Distribution of quinacrine, SN-3294 and SN-7618 in the rat

Drug	Quinacrine	SN-3294	SN-7618
Days of drug administration	10	10	10
Plasma drug concentration, μg./L	134	170	157
Tissue/plasma concentration ratio			
Erythrocytes	2.9	2.9	1.9
Whole blood	7.0	4.1	3.7
Brain	27.6	5.9	31.0
Muscle	194	77	41
Heart	1420	93	150
Kidney	3000	100	670
Lung	4070	150	640
Liver	6380	130	420

tissues of young adult albino rats are given in Table III. Quinacrine has been used as a reference drug. Groups of five animals received daily doses of 25 mg. of drug per kilogram by intubation for a total of ten days. Plasma and tissue samples for the estimation of drug concentrations were obtained 24 hours after the last dose. The group mean concentrations of drug in plasma and various tissues are presented in Table III. These describe the tissue/plasma concentration relationships which obtain in the therapeutic range of plasma drug concentrations.

It is apparent that the concentration of 4-aminoquinolines in tissues greatly exceeds that in the plasma, although less markedly than is the case with quinacrine. The relative concentrations in plasma, erythrocytes and whole blood demonstrate a limited localization in erythrocytes and a greater localization in leucocytes. The value of whole blood drug levels in quantitative pharmacological studies is obviously limited because of the variability of leucocyte counts. Similar results were obtained in the dog. In man, the plasma drug levels following a single intravenous injection of drug indicate that the distribution is qualitatively similar although the metabolic fate may differ somewhat from host to host.

Certain theoretical considerations dealing with relative plasma and tissue drug concentrations require information concerning the extent to which drugs present in the plasma are bound to nondiffusible constituents. The plasma binding of several 4-aminoquinolines and of quinacrine was measured in citrated human plasma at a pH of 7.35 and at 38° C. by dialysis in cellophane bags. The measurements were made at plasma drug concentrations known to be therapeutically effective. The data are summarized in Table IV. It is evident that all of the 4-aminoquinolines are bound to a considerable extent to the nondiffusible constituents of plasma, although SN–10,751 alone is bound to as great a degree as quinacrine. The percentage of drug bound *in vitro* varies widely and systematically with variation in pH, but it is doubtful that changes of practical importance occur within the restricted physiological range of pH observed in the human.

TABLE IV.

Plasma binding of 4-aminoquinolines

Drug	Percentage bound to protein	Plasma drug concentration μg./L
SN-6911	75	700
SN-7135	43	90
SN-7618	55	80
SN-8137	48	105
SN-9584	50	90
SN-10,751	90	125
SN-10,960	52	90
Quinacrine	89	100

TABLE V

Relationship between plasma drug concentration and various daily oral doses of a series of 4-aminoquinolines

Drug	Daily dosage (*mg.*)			
	50	100	200	300
	Mean plasma drug concentration, μg./L			
SN-3294				112
6911			107	179
7135				176
7618	22	49	110	176
8137	16	37	73	98
9584	19	37	68	126
10,751*	3.6	9.3	19	34

* Figures for SN-10,751 include an unknown fraction of degradation product.

The plasma concentration of a chemotherapeutic agent, reflecting the oral dosage and the discrete physiological processes of absorption, distribution, metabolic degradation and excretion, provides a convenient means for following its over-all disposition. In addition, information describing the relationship between oral dosage and plasma drug concentration is necessary in the design of rational regimens of therapy. Data of this type, on each of the 4-aminoquinolines studied, are summarized in Table V for dosage schedules varying from 0.05 to 0.3 gram daily. With daily doses of 0.3 gram, the plasma drug concentrations of six of the drugs are of the same order of magnitude, ranging from 98 μg. per liter for SN–8137 to 179 μg. per liter for SN–6911. However, the concentrations of SN–10,751 are much lower and, in fact, considerably lower than indicated in the table inasmuch as it has been demonstrated that the measurement includes a fluorescent metabolic product. The SN–3294 method also lacks specificity, but there are no data available to indicate what proportion of the measured material is the parent compound.

Since the excretion of drug on serial oral dosage seldom exceeds 25 per cent of the total daily dose, it is apparent that the remainder of the drug undergoes metabolic degradation. No data are avail-

TABLE VI

Rate of disappearance of 4-aminoquinolines from plasma during five-day period

Drug	Number of patients	Plasma concentrations		Percentage remaining at 5 days
		3 hours after last dose	5 days after last dose	
		μg./L	μg./L	
SN-3294	5	214	51	24
SN-6911	4	220	50	23
SN-7135	4	201	56	27
SN-7618	6	28	15	53
SN-8137	10	31	9	29
SN-9584	6	25	10	40

able which describe the rates of degradation of the individual drugs. However, the rates of metabolic degradation and excretion, together with the degree of prior tissue localization, determine the rate at which plasma drug concentrations fall following the termination of therapy. Table VI contains data on the disappearance of the various drugs from plasma during the first five days after a complete course of therapy. All of the drugs studied are present in appreciable concentrations during this period, but SN–7618 has the greatest persistence in the body.

Comment. The 4-aminoquinolines studied are absorbed rapidly and more or less completely from the gastro-intestinal tract. They are localized in various tissues of the body, the degree of localization being intermediate between that of quinacrine and quinine (10, 11). Their excretion is greater that that of quinacrine but seldom exceeds 25 per cent of the total daily dose under ordinary conditions. The mean plasma drug concentrations achieved with standard oral dosage regimens are in the same order of magnitude for the drugs studied. Finally, all persist in the plasma in appreciable quantities for a number of days following the termination of therapy. In suppressive regimens with doses at long intervals, greater persistence as with SN–7618 may offer an advantage.

Section II

SUPPRESSIVE ANTIMALARIAL ACTIVITY

The observations described in this section are concerned with the ability of the various 4-aminoquinolines to terminate clinical attacks of blood-induced vivax and falciparum malaria. Additional studies examine the suppressive activities of three of these drugs in experiments utilizing mosquito-induced vivax infections.

The values for activity obtained in these studies are not considered to be directly applicable to all strains of plasmodia. However, the tests in blood-induced infections utilized strains of *P. vivax* (McCoy) and *P. falciparum* (McClendon) whose susceptibility to quinine and quinacrine is known (12, 13, 14). The testing procedures have been demonstrated to yield reproducible results which define the chemotherapeutic susceptibilities of various strains. Consequently, the activity of related compounds may be compared and related to that of either quinine or quinacrine. Antimalarial activity assayed in this manner is probably a true measure of the ability of an agent to suppress, and to cure, naturally-occurring falciparum malaria and to suppress naturally-occurring vivax malaria.

Procedure. All of the therapeutic tests with blood-induced malaria were performed in accordance with standard procedures previously outlined (12, 13). The regimens of dosage were designed to produce fairly stable plasma drug concentrations during the four-day (vivax) or six-day (falciparum) therapeutic period as in the quinacrine studies (14). Therapeutic results are classified in three groups as previously defined: Class I, no certain effect; Class II, temporary suppression of parasitemia and/or fever; Class III, "permanent" effect, *i.e.*, absence of parasitemia for 14 days (vivax) or 21 days (falciparum) followed by a positive reinoculation to indicate continued host-susceptibility to the infection. The separation of Class II and Class III effects must take into consideration the tendency of these drugs to persist beyond the termination of therapy. The conventions adopted in the design of therapeutic tests in such a situation have been discussed elsewhere (14).

Seven derivatives of 4-aminoquinoline have been tested for their effects on blood-induced infections with the McCoy strain of *P. vivax*. The results are presented in Table VII.

1. *SN–3294.* The study of this drug was limited to observations in eight patients because of its low antimalarial activity. It is the least active of the drugs, as judged either by the oral dosage or by the plasma drug concentration required to produce a given therapeutic effect. The smallest total oral dose which resulted in a Class II effect was 2.1 grams, while doses as large as 1.2 grams failed to exert any certain effect in two of the patients. The lowest mean plasma drug concentration producing a Class III effect

TABLE VII

Relationship between dosage, plasma drug concentration, and therapeutic effect in blood-induced vivax malaria (McCoy strain)

Drug	Total dose	No. of patients on dose	Mean plasma drug concentration (μg./L) classified according to therapeutic result		
			I	II	III
	grams				
	2.7	2			338,321
	2.1	1			257
SN-3294	1.3	2		110,134	
	1.2	2	41,47		
	1.1	1		91	
	1.4	3			164,191,282
	1.0	2			130,191
	0.8	10		63,65,79,81	81,89,109,142, 150,174
SN-6911	0.7	1			99
	0.6	2		54,76	
	0.35	1		54	
	1.1	3			122,181,309
SN-7135	0.6	2		51,65	
	0.3	1	26		
	0.6	1			69
	0.55	1			42
	0.35	2			* *
	0.30	6			14,16,18,20, 22,42
SN-7618	0.275	1			13
	0.225	7	<1	8,10,10	5,11,*
	0.210	2		4,*	
	0.20	2			12,12
	0.13	3	5	2,5	
	0.35	2			10,17
	0.30	6		9.5,12	21,24,27,31
SN-8137	0.225	5		7,11,11,13,17	
	0.15	1		12	
	0.13	1		10	
	0.375	4			8.5,14,23,28
SN-9584	0.30	5		12,15	8.5,8.5,10
	0.225	4		8,9	10,14.5
	0.30	4		7	11,12,18
SN-13,425	0.225	8		5,6,7,9,9,9	10,14
	0.15	2	5,6	*,7	

* Plasma drug concentrations not determined.

was 257 μg. per liter. Class I results were obtained with mean plasma concentrations as high as 47 μg. per liter.

2. *SN–6911.* The relationship between dosage, plasma drug concentration, and antimalarial effect of SN–6911 in 19 patients with blood-induced McCoy vivax malaria is summarized in the table. The activity of this drug is comparable to that of quinacrine on the basis of the dosage required to produce a given effect, *e.g.*, at least 0.7 gram for Class III. However, the minimal plasma SN–6911 concentration which results in Class III effects is approximately three times that of quinacrine.

3. *SN–7135.* This drug received only a limited study in six patients. Further work with the compound did not seem warranted since animal studies demonstrated its toxicity to be considerably greater than that of SN–6911.

4. *SN–7618 (Chloroquine).* Therapeutic tests with this drug in 25 patients are summarized in Table VII. It has the greatest antimalarial activity of the series, both in terms of dosage and of effective plasma concentrations. Total doses as low as 0.2 gram produced Class III effects. The critical plasma drug concentration which divides Class II and Class III effects is approximately 10 μg. per liter, as compared with 25 μg. per liter for quinacrine. Comparison with quinacrine by either standard of reference shows SN–7618 to be two or three times more active.

5. *SN–8137.* This compound is somewhat less active than SN–7618. The data from therapeutic tests in 15 patients are presented in the table.

6. *SN–9584.* The results of 13 tests are presented in Table VII. These reveal it to be a highly active compound. Although the relationship between oral dosage or plasma drug level and therapeutic effect is somewhat erratic within the narrow range of plasma concentrations achieved, it may be concluded that the antimalarial activity of SN–9584 is intermediate to those of SN–7618 and SN–8137.

7. *SN–13,425.* This drug was studied in 16 patients (Table VII). Its activity in man is approximately the same as that of SN–7618.

Four of the more active derivatives of 4-aminoquinoline [4] were selected for trial in blood-induced falciparum malaria of the McClendon strain. The results of tests with the individual drugs are shown in Table VIII. The results in falciparum malaria need not be discussed in detail. As a group, the 4-aminoquinolines show the same high antimalarial activity in falciparum malaria that was demonstrated in vivax malaria. The relative activities of different members of the series would

[4] This group of drugs includes SN-10,751 which was studied in McCoy vivax malaria by Dr. Allan Butler of the Harvard Medical School and which was found to have approximately the same activity as SN-7618 (5).

TABLE VIII

Relationship between dosage, plasma drug concentration, and therapeutic effect in blood-induced falciparum malaria (McClendon strain)

Drug	Total dose	No. of patients on dose	Mean plasma drug concentration (μg./L) classified according to therapeutic result		
			I	II	III
	grams				
	1.7	4		103	124,142,152
	1.4	15	50	65,65,94,94, 95,130,140, 145,197	112,161,164, 166,181
SN-6911	1.3	1			121
	1.2	1			71
	1.1	1			109
	0.9	1			115
	0.7	2		107,110	
	1.0	3			95,113,128
	0.65	3			20,33,54
SN-7618	0.35	10		12,16,18,18	15,18,19,22, 22,27
	0.275	1			16
	0.225	3		10,18	11
	0.65	3			25,39,46
	0.475	1			37
SN-8137	0.45	1			21
	0.425	2			27,28
	0.375	4		13,13,16	19
	0.25	1			19
	0.8	2			36,35
	0.75	1		23	
SN-10,751*	0.65	5		23,23,30	26,41
	0.375	1			28

* Plasma concentrations given are those of total fluorescent material.

appear to be in the same order in the two infections.

At a later date, and after information on the toxicity of these compounds was at hand, further study of their potential use in the routine suppression of malaria was undertaken. These experiments were designed to test the relative effectiveness of three of the more promising members of the group under experimental conditions simulating the use of the drugs as suppressives in the field. They were examined for their suppressive activity in mosquito-induced malaria due to the Chesson strain of *P. vivax*. Chesson vivax malaria differs from McCoy in at least two important respects: (*1*) The erythrocytic parasites are considerably less susceptible to the action of quinine or quinacrine, and (*2*) the mosquito-induced infections are characterized by frequent true relapses beginning as early as one week after the termination of a full course of quinine therapy.

Thirty volunteer subjects [5] were distributed at random into three equal groups. The drugs were administered in single doses of 0.25 gram once weekly for a total of four doses. Malaria was induced by the bites of *A. quadrimaculatus* mosquitoes infected with the Chesson strain of *P. vivax*. Each subject was bitten on three alternate days beginning one week after the first dose of drug, *i.e.*, on the first, third, and fifth days of the second week of drug administration. Subsequent to biting, the salivary glands of the mosquitoes were dissected out, examined for the presence of sporozoites, and the positive glands graded 1 to 4 plus. The inocula, expressed as the total infection densities of mosquitoes biting each subject, ranged from 24 plus to 56 plus with an average of 41 plus. Thick blood smears were examined daily until the appearance of parasites. Blood samples for the estimation of plasma drug concentrations were obtained before and four hours after each drug dose and on the day parasites first appeared in the blood.

The results of this study are summarized in Table IX. With the exception of one subject in the SN–6911 group, all of those exposed to the bites of mosquitoes eventually developed clinical malaria.

TABLE IX

Comparison of suppression by weekly doses of 0.25 gram of SN-6911, SN-7618 and SN-8137 in mosquito-induced vivax malaria (Chesson strain)

	SN-6911	SN-7618	SN-8137
Average inoculum	43+	41+	39+
Ratio of patent infections to number exposed	9/10	10/10	10/10
Appearance of parasites: days after first inoculation			
Range	24–33	43–54	26–33
Average	29	50	29
Days after last dose of drug	15	36	15

Thick blood smears obtained between the 12th and 15th days after the first inoculation revealed small numbers of circulating parasites in three individuals in the SN–6911 group and three in the SN–8137 group. Fever did not accompany this demonstrable parasitemia. Thick blood smears failed to reveal parasitemia in any subject receiving SN–7618. However, when a suit-

[5] This study was conducted at the United States Disciplinary Barracks, Green Haven, New York, with the cooperation of Colonel George Schulz, Lieut. Colonel Nathan Freeman, and Lieut. Colonel Michael D. Buscemi. The subjects were young, healthy volunteers.

able technique for the concentration of parasitized erythrocytes was applied to blood samples obtained during this period, as was to be expected, circulating parasites could be demonstrated in all of the subjects in the three groups (15, 16) except for the one member of the SN–6911 group who never developed clinical malaria. It must be presumed that inoculation had been unsatisfactory in this case.

The shortest prepatent periods[6] in the SN–6911 and SN–8137 groups were 24 and 26 days, respectively. With both of these drugs, parasitemia occurred consistently within 33 days, the average being 29 days. In the SN–7618 group, the shortest prepatent period was 43 days and the average, 50 days. In relation to the last dose of drug, the mean parasite-free intervals were 15 days for SN–6911 and SN–8137 and 36 days for SN–7618. The plasma drug concentrations of all three drugs at the end of the prepatent period were below the minimal effective suppressive level of the drug studied. It appears likely that a weekly dose of 0.25 gram of any one of the three drugs is close to the amount required to provide effective suppression against vivax malaria.

Section III

TOXICITY

The observations described in this section relate to the toxicity of some of the more promising of the 4-aminoquinolines. Five of the more active drugs were studied to determine the daily dose required to produce symptoms when each is administered in progressively increasing dosage.

Materials and methods

Sixty-four volunteers[7] were distributed at random into four equal groups receiving, respectively, SN-7618, SN-8137, SN-9584, and SN-10,751. Thirty-two additional volunteers[5] were divided into two equal groups receiving SN-7618 and SN-13,425 respectively.

[6] Transient parasitemias of low density are disregarded in this instance and the term "prepatent period" is used to indicate the interval from the first inoculation to the appearance of parasites at the onset of clinical malaria.

[7] This study was conducted at the New Jersey State Reformatory, Rahway, New Jersey, with the cooperation of the late Commissioner W. J. Ellis and of Lieutenant W. E. Kulp. The subjects were young, healthy volunteers.

Each individual received an initial priming dose of the drug under study, followed by uniform dosage for a period of one week. The daily dose was increased in step-wise fashion at intervals of one week, each increase being preceded by a booster dose. The amount of drug administered each day was divided into two equal parts, and was taken in colorless capsules at 8 a.m. and 8 p.m. under direct supervision. All doses were calculated as the amount of the base administered. The schedule of dosage is shown in Table X.

TABLE X

Dosage schedule for toxicity study

During the first five weeks the dosage schedules were the same for all five drugs.

Week	Priming dose	Daily dose
	mg.	*mg.*
1	200	50
2	200	100
3	300	200
4	400	300
5	600	400
6	None	*

* SN-8137, 600 mg.
SN-9584, 400 mg.
SN-10,751, 400 mg.
SN-7618, placeboes.
SN-13,425, placeboes.

The desirability of reporting all symptoms was emphasized at the start of the study and an opportunity to report symptoms was offered at the time each dose was administered. However, in order to minimize the factor of suggestion, the subjects were not questioned as to the presence or absence of specific symptoms, except to follow up symptoms previously reported. Each individual was interviewed at the termination of the study and questioned in detail as to his general state of well-being. An attempt was made to elicit any symptoms which had been noted during the period of drug administration.

Adverse reactions

There were sporadic complaints of various symptoms apparently unrelated to the medication throughout the period of the study. These symptoms were usually vague and followed no particular pattern in relation to the drug being taken by the individual. These complaints usually disappeared with the continued administration of increasing doses of medication. The symptoms of intoxication appeared later and showed striking uniformity within any one group.

SN–7618. Twelve of the 32 men who received SN–7618 were asymptomatic throughout the study. Only one subject developed symptoms directly attributable to the drug on a dosage less than 400 mg. per day. This individual complained of spells of light-headedness, dizziness,

and weakness while receiving 300 mg. of SN–7618 daily. The relationship of symptoms to drug was demonstrated by the disappearance of symptoms when placeboes were substituted, and their prompt recurrence when medication was resumed.

Eye symptoms, occurring in 18 of the 32 members of the group, were the most striking and frequent toxic effect noted. These complaints appeared soon after the dose increased to 400 mg. per day. The exact nature of the symptoms was difficult to ascertain. Blurring of vision on looking from near to distant objects, which has been noted in other studies (17), was described definitely by one subject in this group. Most of the others were able to state only that there was something wrong with their eyes, or that they felt heavy, or their vision was blurred.

Generalized itching occurred in one man receiving 400 mg. daily.

All symptoms disappeared within a few days when SN–7618 was replaced by placebo capsules.

SN–8137. There were no symptoms attributable to SN–8137 in 16 men receiving up to 600 mg. of drug daily. A rash which was noted in one volunteer a few days after starting drug, disappeared during continued medication and seemed typical of pityriasis rosea.

SN–9584. Only two men who received SN–9584 remained completely asymptomatic throughout the study. One other had only transient symptoms early in the course of drug administration.

Itching was the most striking complaint of the volunteers receiving SN–9584. This symptom appeared in nine of the 16 men early in the fifth week of drug administration (400 mg. daily). The pruritus involved chiefly the forearms and legs, although in a few it extended to the neck, shoulders, and back. It was most severe at night and was noted by several individuals only at that time. No skin lesion other than excoriation was detectable in any member of the group. The pruritus persisted for variable periods of time after drug was discontinued, being present in some individuals up to three weeks later.

Nausea and vomiting were reported during the last two weeks by four members of the group, three of whom also had pruritus.

Marked nervousness, anxiety, and tremor occurred in three individuals. Two were receiving 400 mg. daily, while the other was receiving a daily dose of only 200 mg. at the time these symptoms developed. In each case, improvement was noted within four to five days despite continued medication.

SN–10,751. Four of the 16 who received SN–10,751 were completely free of symptoms throughout the period of drug administration. Three others had minor complaints of brief duration at some time during the first three weeks of the study, but were free of symptoms during the final three weeks.

The symptoms noted in this group were somewhat ill-defined and non-specific and hence difficult to evaluate in the individual case. However, they did follow a fairly definite pattern and similar symptoms were relatively infrequent in the other groups during the latter part of the study.

Towards the end of the fourth week (300 mg. daily) eight men began to complain of lassitude, lack of energy, and inability to get to sleep at night. Several complained of a feeling of uneasiness in the epigastrium although they did not have definite nausea. Two individuals noted that, although they felt hungry between meals, their appetites disappeared on sitting down to eat. One other subject developed nausea and vomiting while receiving 200 mg. daily. This man had a past history of abdominal cramps and vomiting but it is interesting and possibly significant that the concentration of drug in his plasma was consistently the highest of any in the group.

Symptoms were sufficiently severe so that two men found it necessary to stop working during the last two weeks of the study and a third man refused further medication at the end of the fifth week.

SN–13,425. Six of the 16 men who received SN–13,425 were free of symptoms during the period of drug administration. Itching was the most frequent complaint among those volunteers who exhibited an intolerance to the drug. A total of seven subjects complained of generalized pruritus, four beginning in the third week, one during the fourth week, and two during the fifth week. A skin rash consisting of small, discrete, erythematous papules distributed over the arms, legs, buttocks and scrotum accompanied the itching in four subjects and persisted throughout the remaining period of drug administration.

During the fourth week, two of the subjects

complained of nervousness and a third developed an acute anxiety state. The latter reaction was characterized by flushing of the face, extreme nervousness, insomnia and tremor, which continued for more than one week despite the immediate cessation of therapy.

No significant eye symptoms were noted by the individuals receiving this drug.

DISCUSSION AND SUMMARY

The group of drugs derived from 4-aminoquinoline includes a number of compounds showing high antimalarial activity with potential usefulness in the treatment of human malaria. Changes in the nuclear substituents and changes in the character of the side chain are each accompanied by significant alterations in the physiological disposition, the antimalarial activity, and the toxicity of the resulting compounds.

The 4-aminoquinolines showing the most marked antimalarial activity in both avian and human malaria are derived from 7-chloro-4-aminoquinoline. The best combination of high activity and low toxicity was found in either SN–7618 or SN–8137. Both have advantages over quinacrine in their lower toxicity and in the smaller dosage or plasma drug concentration required to produce a given effect. Although SN–8137 is considerably less toxic than SN–7618, it is also somewhat less active. Administration of SN–7618 for over a year has shown it to be a safe suppressive agent when the recommended dosage is used (18). Either drug is useful for routine suppression, but it would appear from the data derived from the field-type suppressive study that SN–7618 has a considerable margin of efficacy because of its greater activity and persistence.

Dosage regimens which should be suitable for the suppression of malaria and for the treatment of acute attacks were chosen on the basis of the data presented in this paper. Work based on these suggested regimens has already been published (19, 20) and confirms the conclusions drawn from the experimental data.

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