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Efficacy of Intramuscular Amopyroquin for Treatment of *Plasmodium falciparum* Malaria in the Gabon Republic

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The efficacy of a 12-mg/kg (of body weight) intramuscular amopyroquin (ApQ) regimen (two successive 6-mg/kg injections at a 24-h interval), previously established from kinetic studies on healthy volunteers and multicenter studies on patients with malaria, was investigated in 152 patients (children and adults) in Gabon with *Plasmodium falciparum* malaria. All children in the present study (ages, 1 to 14 years) showed higher degrees of parasitemia and temperatures and lower hematocrit values than did adults at the time of admission. No major side effects in the patients were observed. On day 7, all patients were apyretic; clearance of parasites was obtained in 143 of 152 patients (94%); a low level of parasitemia was observed in nine patients, all of whom were children (6%). In vitro chemosusceptibility tests carried out on *P. falciparum* isolates from patients demonstrated 51% of resistance to chloroquine (Cq). A correlation was found between the in vitro chemosusceptibilities to Cq and ApQ, but no relationship between the in vitro activity and the in vivo efficacy of ApQ could be found. Concentrations of ApQ in blood assayed by high-performance liquid chromatography on day 2 did not differ significantly between the groups in whom therapy was a success or a failure, although the mean ApQ concentration in blood for the group that failed therapy was 31% lower. Concentrations greater than 100 nmol of self-prescribed Cq and amodiaquine per liter, which were assayed simultaneously with ApQ, were observed in 78 patients (51%). They did not correlate with degrees of parasitemia compared with ApQ alone, which did. Successful treatment by day 7 was obtained in 69 of 74 patients (93%) who had no other 4-aminoquinolines in their blood. The results of the present study show that an ApQ regimen of 12 mg/kg over 2 days may be an alternative for the treatment of Cq-resistant malaria, at least in adult patients, in the field.

Amopyroquin (ApQ) is a 4-aminoquinoline which is structurally related to amodiaquine (Aq) and which was demonstrated nearly 30 years ago to be effective in the treatment of *Plasmodium falciparum* and *Plasmodium vivax* malaria when given as a single 3-mg/kg (of body weight) intramuscular injection (7, 8, 14). After being abandoned in favor of chloroquine (Cq) and then Aq, interest in ApQ is now renewed following the extensive development of resistance to Cq and the appearance of severe side effects with Aq after prolonged prophylaxis (2, 6). Since no pharmacokinetic studies of ApQ were available, we initially studied its metabolism and kinetics in the rat and rabbit (13) and then in healthy human volunteers (16), using the dosage of 3 mg/kg, which was initially effective. At the same time, multicenter studies in patients with acute malaria showed a poor efficacy when 3 mg/kg was used (16% in Gabon [n = 79]; 25% in Madagascar [n = 12]) and when 6 mg/kg was used (42% in Gabon [n = 25]) and only partial efficacy when 6 and 3 mg/kg were used at a 24-h interval (83% in Gabon [n = 23]; 80% in Cameroon [n = 78]) (10). From the results of those clinical trials and the results of a kinetic study in healthy subjects (16), we proposed the following regimen as being potentially therapeutic: two intramuscular injections of 6 mg/kg each at a 24-h interval.

The aim of the present study was to evaluate the efficacy and tolerance of this regimen in both children and adults in Gabon infected with *P. falciparum*. The prevalence rate of clinical resistance to Cq in Gabon was supposed to be intermediate.

MATERIALS AND METHODS

Study patients. One hundred seventy-five patients attending out-patient clinics in a hospital in Mounana, Gabon, were recruited for the study from May to November 1989, after receiving approval for the study from the Ethical Committee of the Health Ministry of Gabon and informed consent from the patients or the parents or guardians of the children. The patients enrolled in the present study fulfilled the following criteria: age of over 1 year, a history of fever or rectal temperature of ≥38°C, and more than 1,000 asexual *P. falciparum* parasites detected per μl of blood. Exclusion criteria were clinical evidence of severe malaria, as follows: impaired consciousness, prostration or convulsions, acute dehydration, and suspicion of pregnancy and previous adverse reactions to 4-aminoquinolines. On admission, the presence of other 4-aminoquinolines self-prescribed by the patients was evaluated by a urine test with a detection limit of 10 μmol/liter (1). Of the 175 patients initially recruited for the study, 6 were eliminated because no follow-up of drug levels on day 2 was possible and 17 others were eliminated because their parasite count was not available on day 7. The total number of patients in the study group was thus 152.

Study design. The 152 patients were given two intramuscular injections of 6 mg of ApQ base (Parke-Davis, Courbevoie, France) per kg of body weight, with a 24-h interval (days 0 and 1) between the two injections. The patients were

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TABLE 1. Characteristics of patients on admission

Group (age [yr]); no. of subjects	Mean parasitemia (no. of parasites/μl [range])[a]	Hematocrit (% [mean ± SD])	Temp (°C) [mean ± SD])
1 (1–4; 77)	52,284 ×/÷ 3.866 13,524–202,128)	32.6 ± 5.6	38.9 ± 1.0
2 (5–14; 51)	35,264 ×/÷ 2.954 (11,936–104,170)	33.5 ± 5.5	39.1 ± 1.0
3 (>14; 24)	8,436 ×/÷ 2.769 (3,046–23,363)[b]	36.8 ± 5.3[b]	38.1 ± 0.8[b]
Total (n = 152)	34,347 ×/÷ 3.417 (10,052–117,360)	33.6 ± 5.6	38.8 ± 1.0

[a] Values are geometric means [exp (SD of log values)] and means multiplied and divided by exp (SD of log values), i.e., a 68% confidence interval.
[b] $P < 0.05$ compared with groups 1 and 2. Exact probabilities of the significance level are given in the text and are from the Bonferroni adjusted t test.

hospitalized during the first 2 days for attentive clinical care. Administration of the drug and a 7-day clinical follow-up were carried out by the same physician.

Tolerance. Side effects actively sought out by the physician and reported by the patients (or the parents or guardians for the children) and the assessment of each patient's health by the physician were recorded.

Clinical and biological investigations. Clinical status, rectal temperature, and hematocrit values were recorded on days 0, 2, and 7. The in vitro chemosusceptibilities of the parasite isolates to Cq and ApQ were assessed on day 0 by a semimicrotest that measured the incorporation of tritiated hypoxanthine (11). Quantitative asexual parasite counts were determined on Giemsa-stained thick blood smears on days 0, 2, and 7. ApQ concentrations in whole blood were measured on day 2 by a high-performance liquid chromatographic (HPLC) method (12). Because of frequent and often heavy self-medication with Cq and Aq (17), the most available and most widely used drugs in Gabon, these drugs and their respective metabolites were simultaneously checked with ApQ by HPLC on day 2, in addition to the day 0 urine 4-aminoquinoline detection test, the sensitivity of which was lower than that of the HPLC assay.

Statistical analysis. Results were expressed as means ± standard deviations (SDs) for all variables except parasitemia and drug concentrations in blood, which were given as geometric means, exponential (exp) (SD of log values), and the means were multiplied and divided by exp (SD of log values), i.e., a 68% confidence interval. In the groups of the lowest size, mean, minimal, and maximal values were given. Data were analyzed statistically by using one-way and two-way analyses of variance (with Bartlett's test for equal variance) without or with covariates and simple and multiple regression analyses (15). When significant differences were found between more than two groups by variance analysis, each interesting pair of groups was compared by the Bonferroni adjusted t test (4). The Mann-Whitney nonparametric U test was used for nonnormally distributed values. Differences in values were considered significant if the P value was ≤ 0.05 or 0.05 divided by the number of tests made. For categorical variables, the comparison was made by using the χ^2 test or Fisher's exact test for the comparison of two proportions and the χ^2 test for trend (Kendall's Tau B). The level of significance was also 0.05.

RESULTS

Characteristics of patients. Table 1 describes the characteristics of the patients at the time of admission to the study (day 0). The 152 patients were distributed into the following three groups according to age: group 1, from 1 to 4 years (n = 77); group 2, from 5 to 14 years (n = 51); group 3, over 14 years (n = 24).

Of 152 urine tests carried out, 35 (23%) were positive for 4-aminoquinolines. Patients whose urine tests were positive were nevertheless maintained in the study in order to check the efficacy of ApQ under the field conditions of Africa. The geometric mean of initial parasitemia was 34,347 parasites per μl of blood (range, 10,052 to 117,360 parasites per μl of blood) for the whole group. Higher initial parasitemias were observed in groups 1 (mean, 52,284 parasites per μl of blood; range, 13,524 to 202,128 parasites per μl of blood) and 2 (mean, 35,264 parasites per μl of blood; range, 11,936 to 104,170 parasites per μl of blood) than in group 3 (mean, 8,436 parasites per μl of blood; range, 3,046 to 23,363 parasites per μl of blood) ($P < 10^{-5}$ and $P < 10^{-4}$, respectively). The mean hematocrit value for the entire group was 33.6% ± 5.6%. This value in groups 1 (32.6% ± 5.6%) and 2 (33.5% ± 5.5%) was significantly lower than that in group 3 (36.8% ± 5.3%) ($P = 0.002$ and $P = 0.014$, respectively). The mean rectal temperature for the total group of patients was 38.8 ± 1.0°C. It was significantly higher in groups 1 and 2 (38.9 ± 1.0 and 39.1 ± 1.0°C, respectively) than in group 3 (38.1 ± 0.8°C) ($P = 0.0002$).

In vitro testing. Of all the Cq and ApQ semimicrotests carried out, 63 were successful. Resistance to Cq, which was defined as the concentration greater than 100 nmol/liter required to inhibit growth of 50% of parasites (IC_{50}), was observed in 32 isolates (51%). Mean IC_{50}s were 12 ± 6 nmol/liter for ApQ and 139 ± 108 nmol/liter for Cq and correlated with each other: 32% of the variation of the IC_{50} of ApQ was explainable by the IC_{50} of Cq (and vice versa) ($r = 0.564$; degrees of freedom = 61; $P < 10^{-5}$).

In vivo testing. (i) Tolerance analysis. No major side effects were reported by the patients after questioning by the physician, and none were observed after physical examination. Mild adverse reactions consisting of pain at the site of injection lasting some 2 h after each injection were reported by almost all patients, but the pain disappeared spontaneously.

(ii) Evolution of parasitemia, temperature, and hematocrit. After ApQ treatment, no parasites were found in 143 of 152 patients (94%) by day 7; those 143 succeeding patients were spread out among 70 patients in group 1 (91%), 49 patients in group 2 (96%), and 24 patients in group 3 (100%); respective percentages of treatment successes seemed to be related to age (χ^2 test for trend, $P = 0.073$). Of the nine patients who failed therapy (6%), seven were in group 1 (9%) (the geometric mean [and the minimal and maximal values, or range] of parasitemia were 327 [8 to 900] parasites per μl of blood) and two were in group 2 (4%); the individual parasitemias in the group 2 patients were 144 and 450 parasites per μl of blood, respectively.

No significant difference in initial parasitemia was observed between the two groups representing treatment success (mean, 32,500 parasites per μl of blood; range, 8,560 to 123,340 parasites per μl of blood) and failure (mean, 82,710 parasites per μl of blood; range, 15,490 to 441,610 parasites

TABLE 2. ApQ concentrations in blood assayed on day 2[a]

Group (age [yr])	ApQ concn (nmol/liter [range]) for treatment:		
	Success	Failure	Total
1 (1–4)	141 ×/÷ 1.956 (72–276) (n = 70)[b]	103 ×/÷ 2.107 (49–217) (n = 7)	137 ×/÷ 1.971 (70–270) (n = 77)
2 (5–14)	173 ×/÷ 1.889 (92–327) (n = 49)	121 (113–129) (n = 2)	171 ×/÷ 1.873 (91–319) (n = 51)
3 (>14)	172 ×/÷ 2.113 (81–363) (n = 24)	(n = 0)	172 ×/÷ 2.113 (81–363) (n = 24)
Total	156 ×/÷ 1.965 (80–307) (n = 143)	107 ×/÷ 1.916 (56–204) (n = 9)	153 ×/÷ 1.932 (79–295) (n = 152)

[a] Data are expressed as geometric mean [exp (SD of log values)] and the mean multiplied and divided by exp (SD of log values), i.e., a 68% confidence interval.
[b] n indicates number of patients.

per μl of blood) (P = 0.16) by day 7. In the group in which treatment was a success (n = 143), 102 patients had already cleared their parasites by day 2, whereas 41 (29%) were still parasitemic (mean, 186 parasites per μl of blood; range, 40 to 860 parasites per μl of blood). In the same way, of the nine patients who failed therapy, five had already cleared their parasites by day 2, whereas the other four (44%) were still parasitemic (mean, 1,800 parasites per μl of blood; range, 650 to 4,990 parasites per μl of blood). The mean parasitemia in the group that failed therapy (1,800 parasites per μl of blood) was significantly greater than that in the group in which treatment was a success (186 parasites per μl of blood) (P = 0.001).

On day 0, no difference in the mean rectal temperature was observed between the groups in which treatment was a success (38.9 ± 1.0°C) and a failure (38.7 ± 1.1°C). It was the same for the hematocrit values between the groups in which treatment was a success (33.6% ± 5.0%) and a failure (32.3% ± 5.6%).

On day 2, compared with the values at the time of admission, the rectal temperature had decreased significantly and was significantly lower in the group in which treatment was a success (37.0 ± 0.5°C) than in the group in which treatment was a failure (37.7 ± 1.1°C) (P = 0.0005). Among the 45 patients who were parasitemic on day 2, 41 patients (group in which treatment was a success) were apyretic (37.0 ± 0.2°C) and differed from the other 4 patients (group in which treatment was a failure) whose mean temperature was 38.6 ± 0.8°C ($P < 10^{-7}$). Compared with the values at the time of admission, hematocrit values decreased similarly in both groups: 31.9% ± 6.8% and 30.9% ± 4.6% in the groups in which treatment was a success and a failure, respectively.

On day 7, the temperatures of the groups in which treatment was a success (36.9 ± 0.3°C) and a failure (37.1 ± 0.4°C) did not differ (P = 0.13). On the contrary, in the group in which treatment was a success, hematocrit values (34.0% ± 6.2%) were found to be similar to those obtained on day 0, but in the group in which treatment was a failure, hematocrit values continued to decrease (28.4% ± 5.2%), exhibiting significantly lower values than those in the former group (P = 0.037). Among the 45 patients who were parasitemic by day 2, 41 patients (group in which treatment was a success) had a mean hematocrit value of 32.1% ± 6.3%, which differed from that of the other 4 patients (group in which treatment was a failure), 24.0% ± 2.2% (P = 0.014). Furthermore, the hematocrit values of the seven patients of group 1 who failed therapy (27.3% ± 4.4%) differed from the hematocrit values of the children in the same group in whom therapy succeeded (32.1% ± 6.2%) (P = 0.049).

(iii) Drug concentrations in blood. Mean ApQ concentrations in blood assayed on day 2 did not differ significantly between the groups in which treatment was a success (mean, 156 nmol/liter; range, 80 to 307 nmol/liter; n = 143) and failure (mean, 107 nmol/liter; range, 56 to 204 nmol/liter; n = 9) (Mann-Whitney nonparametric U test, P = 0.068). No significant differences were found between groups 1 (mean, 137 nmol/liter; range, 70 to 270 nmol/liter; n = 77), 2 (mean, 171 nmol/liter; range, 91 to 319 nmol/liter; n = 51), and 3 (mean, 172 nmol/liter; range, 81 to 363 nmol/liter; n = 24) (P = 0.072) or between individuals of different ages within the groups in which treatment was a success or failure (Table 2).

Significant self-medication represented by a concentration over 100 nmol of Cq plus monodesethylchloroquine plus monodesethylamodiaquine per liter of blood on day 2 was observed in 51% of the 152 patients (41 group 1 patients, 53%; 28 group 2 patients, 55%; and 9 group 3 patients, 38%). This self-medication did not differ between the groups in which treatment was a success or failure (P = 0.60) or between the absence or presence of parasites by day 2 (P = 0.68).

(iv) Parasitemia and drug concentration relationship. Simple and multiple regression analyses in the group with parasites on day 2 (n = 45) showed a significant negative correlation (r = −0.425; degrees of freedom = 43; P = 0.0036) between the degree of parasitemia and ApQ concentrations on day 2 but no correlation with the total self-prescribed drugs (r = 0.242; degrees of freedom = 43; P = 0.1090). Parasite clearance was obtained in 69 of 74 patients (93%) who had no other 4-aminoquinolines in their blood.

(v) Patients who failed therapy. The individual biological characteristics of the nine patients who failed therapy and whose parasites were cleared or not cleared by day 2 are given in Table 3.

DISCUSSION

The ApQ regimen described here (two successive i.m. injections of 6 mg/kg at a 24-h interval) was well tolerated except for a pain sensation at the injection site, which disappeared spontaneously. Hepatic enzyme levels were not determined since, after using Aq, hepatic cytolysis was observed only after a long period of prophylaxis with Aq and never after a 3-day treatment. The regimen described here led to a temperature normalization in all patients and a parasite eradication rate of 94% by day 7. In all patients, ApQ induced a decrease in rectal temperature, but it did so more rapidly in patients in the group in which therapy succeeded and those who were aparasitemic on day 2. The persistence or reappearance of parasites in blood was always associated with a lower hematocrit value, which mainly reflected the level of parasitemia, as confirmed by the difference in hematocrit values (on day 7) of the children who succeeded or failed therapy. Among the patients, who failed therapy, however, those who were parasitemic on day

2 must have kept their parasites for the entire 7-day period, since their hematocrit values had still decreased by day 7.

Follow-up of the patients was limited to 7 days, because it is always difficult in the field to assume that follow-up will occur after day 7 and to distinguish between recrudescence of or reinfection by parasites. The level of resistance to Cq of the parasite strains which infected these patients was defined by in vitro drug susceptibility tests which demonstrated a resistance rate of 51%. An in vivo study simultaneously conducted with a sample of 34 patients from a population similar to that used in the present study in Mounana, Gabon, during the same period showed a 56% level of clinical resistance to Cq with the standard 3-day 25-mg/kg Cq regimen (5).

The patients who failed therapy (Table 3) were all apyretic and showed a low level of parasitemia by day 7. Only four of the patients had a hematocrit less than or equal to 27%. All were children less than 7 years old. It can be pointed out that all children in the present study (groups 1 and 2) were already different from the adults (group 3) in terms of parasitemia, hematocrit, and temperature status, which corresponded to a greater infection burden, then a more severe illness. This could partly be due to the lower level of immunity in children in areas endemic for *P. falciparum* malaria. Nevertheless, a similar level of immunity did not lead to treatment failure in all patients concerned, since 70 children ages 1 to 4 years (91%) and 49 other children ages 5 to 14 years (96%) successfully responded to treatment by day 7.

The correlation found between the in vitro IC_{50}s of Cq and ApQ might suggest a cross-susceptibility between the two drugs, but up to now, no in vitro IC_{50} of ApQ can be related to an in vivo treatment failure and there is still no evidence of in vivo clinical resistance to ApQ.

The levels of ApQ in blood obtained with the regimen described here 24 h after the second injection were lower than the theoretic value predicted by concentration-time curve models obtained from Caucasian, adult, and healthy volunteers (16). Ethnicity, age, and disease-related factors may contribute to these differences. Despite the heterogeneity of the population studied, no differences in blood ApQ levels were observed between the three age groups, and no correlation was found between blood ApQ concentrations and the age of the patients, suggesting a similar bioavailability of the drug in the overall population. In our study, self-medication was similarly distributed between the groups in which treatment was a failure and success, a result which minimizes involvement of this factor but underlines the necessity of using sensitive and specific tools for monitoring simultaneously the other most widely used malaria-related drugs in blood. There was a clear-cut relationship between ApQ levels and parasite counts on day 2 and a trend among the patients who failed therapy to have a lower ApQ concentration in their blood, even if this difference was not statistically significant. This lower ApQ level probably reflects an impaired disposition of the drug in the children who failed therapy.

Moreover, because the stage and synchronicity of the infecting parasite population are determinants of an immediate therapeutic response, the time of administration of antimalarial agents with widely fluctuating concentrations (as was the case for ApQ) could influence treatment efficacy (18). This improved efficacy of timed chloroquine treatment was recently demonstrated in *P. falciparum*-infected patients (the midterm trophozoites of *P. falciparum* being the

TABLE 3. Biological characteristics of the nine patients who failed therapy

Parasites:	Age (yr)	No. of parasites/μl of blood on day:			Hematocrit (%) on day:			Temp (°C) on day:			ApQ concn (nmol/liter) on day 2	Cq + CqM1 + AqM1 concn (nmol/liter) on day 2[a]	IC_{50} (nmol/liter)	
		0	2	7	0	2	7	0	2	7			Cq	ApQ
Cleared by day 2	1	126,000	0	450	38	40	34	37.6	36.8	37.6	288	104	340	23
	2	2,700	0	900	32	28	30	37.2	36.8	36.5	85	241		
	2	40,500	0	270	32	27	28	39.5	36.5	36.8	35	10		
	3	661,500	0	8	40	32	30	39.5	38.2	37.6	129	42	53	12
	5	22,500	0	450	35	30	38	37.6	36.7	37.3	129	34		
Not cleared by day 2	2	157,500	680	560	26	30	23	40.5	39	36.8	58	84	149	15
	2	288,000	4,500	900	22	25	22	38.8	37.5	36.8	83	412		
	2	333,000	900	900	32	36	24	38.9	39.3	37.5	230	293	50	9
	6	58,500	3,800	144	34	30	27	38.8	38.5	37.3	113	16		

[a] Cq, chloroquine; CqM1, monodesethylchloroquine; AqM1, monodesethylamodiaquine.

most susceptible stages to Cq) (9). The susceptibility of the parasite to ApQ might be also stage dependent.

It is likely that the conjunction of all of these factors, particularly the large parasite burden, low level of immunity, and impaired drug disposition, combined with an inadequate parasite stage for effective attack, was responsible for the treatment failure in these children. Therefore, in order to state the efficacy of this drug for all patients with malaria, further studies in very young children are required.

Nevertheless, the ApQ regimen described here was well tolerated and proved its efficacy in partly immune patients in an area of Gabon where a 56% prevalence rate of clinical resistance to Cq has been observed. ApQ may be an alternative treatment for patients with malaria who need to receive drugs by the parenteral route and for the treatment of Cq-resistant malaria, at least in adult patients, in the field.

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