Efficacy and pharmacokinetics of a new intrarectal quinine formulation in children with *Plasmodium falciparum* malaria

H. BARENNE,¹ E. PUSSARD,² A. MAHAMAN SANI,³ F. CLAVIER,² F. KAHATANI,⁴ G. GRANIC,⁴ D. HENZEL,² L. RAVINET⁵ & F. VERDIER²

¹Coopération Française, Ministère de la Santé Publique du Niger, ²Institut National de la Santé et de la Recherche Médicale, Unité 13/Institut de Médecine et d'Epidémiologie Africaines et Tropicales, Paris, ³Faculté des Sciences Médicales de Niamey, Niger, ⁴Hôpital de Niamey and ⁵Sanofi Winthrop, Gentilly, France

- 1 Three groups of seven children aged 2–14 years with acute uncomplicated *Plasmodium falciparum* malaria received 12.8 mg kg⁻¹ quinine gluconate by the intrarectal route (new cream formulation) or 8 mg kg⁻¹ Quinimax[®] (a Cinchona alkaloid combination) by the intramuscular or intravenous (4 h infusion) route every 8 h for 3 days. Clinical and parasitological status was similar in the three groups at enrolment.
- 2 At 36 h, body temperature of all children of the three groups was returned to normal and remained so until day 7.
- 3 The decrease in parasitaemia did not differ between the three groups and the time required for a 50% fall in parasitaemia relative to baseline was 12.3 ± 5.4, 18.2 ± 6.1 and 14.5 ± 4.2 h in the intrarectal, intramuscular and intravenous treatment groups, respectively. Parasitaemia expressed as a percentage of initial values was not significantly different in the three groups after 48 h of treatment (7.4 ± 16.0, 4.1 ± 4.2 and 2.2 ± 3.8% in the intrarectal, intramuscular and intravenous treatment groups, respectively). All the patients were aparasitaemic by day 7.
- 4 The tolerability of the three treatments was good; in particular, no rectal irritation was reported with the cream formulation.
- 5 The $t_{\max}$ occurred later after intrarectal (4.1 ± 2.4 h) and intravenous infusion (3.8 ± 0.5 h) than after intramuscular injection (1.6 ± 1.3 h) ($P=0.02$). $C_{\max}$ was lower with the intrarectal (3.0 ± 1.0 mg l⁻¹) and intramuscular routes (3.2 ± 0.7 mg l⁻¹) than with the intravenous route (5.1 ± 1.4 mg l⁻¹) ($P=0.003$). Areas under the curve (AUC(0, 8 h)) were smaller with the intrarectal (17.0 ± 7 mg l⁻¹ h) and intramuscular routes (19.4 ± 4.8 mg l⁻¹ h) than with the intravenous route (27.8 ± 8.2 mg l⁻¹ h) ($P=0.02$). The approximate bioavailability of intrarectal quinine from 0 to 8 h was 36% *vs* intravenous quinine and 51% *vs* intramuscular quinine.
- 6 The good tolerability and efficacy of this new intrarectal quinine formulation outweigh its low approximate bioavailability. This new approach might thus be a safe and effective alternative to intramuscular quinine injection for the treatment of children with acute uncomplicated *Plasmodium falciparum* malaria in the field.

Keywords *falciparum* malaria children intrarectal quinine cream efficacy pharmacokinetics

Correspondence: Dr F. Verdier, INSERM Unité 13/IMEA, Hôpital Bichat-Claude Bernard, 46 Rue Henri Huchard, 75877 Paris, Cedex 18, France

Introduction

In a previous study, we evaluated the clinical and parasitological efficacy and bioavailability of intrarectal Quinimax® (a Cinchona alkaloid combination) in children with *Plasmodium falciparum* malaria in Niger [1]. The rectal route was used to avoid the numerous complications associated with intramuscular quinine administration [2–8]. Intrarectal administration of 20 mg kg⁻¹ of the diluted injectable formulation of Quinimax® showed similar efficacy to that of intramuscular administration, in terms of fever and parasitaemia clearance times, but the product, which had to be diluted because of its very low pH, was sometimes expelled from the rectum, thereby reducing the dose absorbed; in addition, the calculated intrarectal bioavailability was only 40%.

A cream formulation (SR 26017C) with a pH of 4.5 has now been specifically designed for the intrarectal route, with a view to minimizing possible local side-effects, improving the simplicity of use, and increasing the bioavailability of intrarectal quinine.

The aim of this work was to study the clinical and parasitological efficacy, and pharmacokinetics, of this new formulation in children with *P. falciparum* malaria, relative to intramuscular and intravenous injections.

Methods

Patients

The study took place in the children's ward of Niamey hospital, Niger, between July and December 1993 (a permanent malaria transmission period). Chloroquine resistance in Niger has been documented *in vitro* [9] and *in vivo* [10], but *P. falciparum* is still sensitive to quinine. Twenty-one children aged from 2 to 14 years were enrolled in this randomized open-label study. Inclusion criteria were the presence of more than 1000 asexual *P. falciparum* parasites µl⁻¹ of blood, acute malaria with vomiting, slight coma (with score higher than 12 of the Glasgow classification, i.e. confusion in time and space, clouding consciousness, agitation as a result of severe illness but without neurological symptoms of cerebral malaria), and restlessness or convulsions warranting parenteral therapy. Full informed consent was given by a parent or guardian. Exclusion criteria were coma with score lower than 12 of the same Glasgow classification, diarrhoea, other documented causes of fever and drug treatment of malaria within the preceding week. Non included children received Quinimax® infusions. The study was approved by the ethics committee of the Niger Health Ministry.

Drug administration

Quinine was administered in one of three ways, defining three groups of children.

In group 1 seven children were given 12.8 mg quinine

gluconate kg⁻¹ body weight intrarectally as a new quinine cream (Sanofi, Gentilly, France). The new intrarectal cream (SR 26017C) contains 5.33 g quinine gluconate per 100 g of cream, the pH of which is 4.5. It is presented as a graduated syringe-nozzle containing 3.75 g of cream, corresponding to 200 mg of quinine gluconate, and 125 mg of quinine base. Then the 12.8 mg kg⁻¹ quinine gluconate administered to the children correspond to 8 mg kg⁻¹ quinine base. The vehicle used in this cream was constituted of sodic methyl *p*-hydroxybenzoate, sorbic acid, oleic and palmitic glycerides and purified water. The stability of the cream was studied up to 35° C: no variation in the quinine titre was observed over 6 months. Considering the weights of children, volume of cream administered ranged from 1 to 5 ml.

In group 2, seven children were given 8 mg Quinimax® kg⁻¹ body weight intramuscularly as a deep injection in a lateral thigh muscle. Quinimax® is a water-soluble combination of Cinchona alkaloids containing 96.1% quinine, 2.5% quinidine, 0.68% cinchonine and 0.67% cinchonidine (Quinimax®, Sanofi, Gentilly, France). The dosage of 8 mg kg⁻¹ Quinimax® corresponded to 4.7 mg kg⁻¹ quinine base.

In group 3, seven children were given 8 mg kg⁻¹ Quinimax® administered as a slow intravenous infusion over 4 h. As in group 2, the dosage of 8 mg kg⁻¹ Quinimax® correspond to 4.7 mg kg⁻¹ quinine base. All administrations were performed every 8 h for 3 days.

Clinical and laboratory data

Physical signs and rectal temperature were recorded at inclusion and twice-daily until temperature fell to 37° C, then once daily until the end of the week.

May-Gründwald-Giemsa-stained thick and thin films were prepared by finger prick before treatment and 4, 8, 16, 24, 32, 48 h and 7 days after starting treatment. Parasitaemia was assessed by counting asexual parasites relative to red blood cells (RBC) in thin films (200 RBC/field and 100 fields); each sample was counted by two different technicians.

Drug assays

Blood (1 ml) was collected in sterile EDTA tubes before treatment and 0.5, 1, 3, 4, 6, 8, 12, 16, 24, 32, 40 and 48 h after starting therapy. Blood was stored at -30° C until analysis at INSERM Unit 13 (Paris, France). Specific quinine base blood concentrations were determined by means of high-performance liquid chromatography with fluorometric detection, using quinidine as internal standard [1]. In order to verify the possible interference of other Cinchona alkaloids with the internal standard, each blood sample was extracted twice, with and without internal standard addition. No interference was found, the limit of sensitivity being 0.05 mg l⁻¹ whole blood using a 100 µl sample. Calibration curves were linear (*r*=0.99) in the range 0.1–10 mg l⁻¹. Extraction recovery from whole blood

was 77 and 71% at concentrations of 1 and 10 mg l⁻¹ respectively. Coefficients of variation were 6.2 and 7.5% (within day) and 7.1 and 8.2% (day to day), at concentrations of 1 and 10 mg l⁻¹ respectively.

Pharmacokinetic analysis

Whole-blood concentrations of quinine were fitted using an iterative least-squares curve-fitting programme (APIS) [11]. The best fit of concentration *vs* time data was obtained using a one-compartment model. Peak concentrations ($C_{\max}$) and the time to peak concentration ($t_{\max}$) were observed values. The area under the time-concentration curve (AUC(0, 8 h)) was calculated according the linear trapezoidal rule. An approximate estimation of bioavailability of the intrarectal route was calculated as the ratio of the intrarectal AUC to the intravenous or intramuscular AUC from 0 to 8 h.

Side-effects

Side effects were reported by the patients (or the parents or guardians), and actively sought by the attending physician. Particular attention was turned to the anal status of the children.

Statistical analysis

Results are expressed as means $\pm$ s.d. and range, except in Figure 2 where the points are plotted as means $\pm$ s.e.mean. Taking into account the small size of the children sample in each group, a non parametric Kruskal–Wallis's test was used to compare the results obtained with the three routes of administration. Bartlett's test was used to verify the homogeneity of variances. *P* values <0.05 were regarded as statistically significant.

Results

Clinical and laboratory data

The baseline clinical findings and parasite counts in the three groups of children are summarized in Table 1. No differences were observed in terms of age, weight, temperature or parasitaemia between the three groups at enrolment. The time course of rectal temperature was similar in all three groups. At 36 h, rectal temperature of all children of the three groups was returned to normal and remained so until day 7. The time course of parasitaemia (Figure 1) was similar in the three groups, as evidenced by similar times for a 50% fall in parasitaemia relative to baseline (12.3 ± 5.4 , 18.2 ± 6.1 and 14.5 ± 4.2 h in the intrarectal, intramuscular and intravenous treatment groups, respectively). Given the variability in parasitaemia clearance time and the sample size (7 patients per group), the lowest degree of difference observed with a probability of 90% (risk $\alpha=0.05$ and risk $\beta=0.1$) was calculated to 8 h. Moreover, no differences were observed in parasitaemia at 48 h expressed as a percentage of baseline values (7.4 ± 16.0 , 4.1 ± 4.2 and $2.2 \pm 3.8\%$ for the intrarectal, intramuscular and intravenous treatment groups, respectively). All the children were aparasitaemic on day 7.

Side effects

The tolerability of the three routes of administration was good. After intrarectal administration no rectal irritation was reported. Because of the consistency of the cream, the latter was never expelled and did not ever lead to any diarrhoea. The intramuscular injections caused slight pain at the site of injection which disappeared spontaneously within a few hours.

Pharmacokinetic results

The mean quinine whole blood concentration–time curves obtained with the three routes of administration

Table 1 Baseline clinical and laboratory findings (mean $\pm$ s.d., except for parasitaemia: geometric mean and range) in 21 children with acute uncomplicated *P. falciparum* malaria in Niger

	Intrarectal administration (n = 7)	Intramuscular administration (n = 7)	Intravenous administration (n = 7)
Age	108.0	126.9	86.0
(months)	48.5	28.4	45.3
Weight	21.6	28.6	24.1
(kg)	8.0	12.2	9.4
Temperature	38.6	38.7	38.1
(°C)	1.4	0.4	0.7
Parasitaemia*	42,210	67,570	42,960
(parasites μ l ⁻¹)	10,520–169,370	14,750–309,500	13,020–141,710

* Geometric mean and range

Figure 1 Decline in parasitaemia expressed as percent of values relative to baseline after a) intrarectal administration of 12.8 mg kg^{-1} quinine gluconate (cream formulation) (i.e. 8 mg kg^{-1} quinine base) and b) intramuscular or c) intravenous administration of 8 mg kg^{-1} Quinimax® (i.e. 4.7 mg kg^{-1} quinine base) in children with falciparum malaria.

are illustrated in Figure 2. Quinine pharmacokinetic parameters are reported in Table 2. t_{max} (median, range) occurred later with the intrarectal (4.0, 1.0–8.0 h) and intravenous routes (4.0, 3.0–4.2 h) than with the intramuscular route (1.2, 0.6–4.0 h) ($P=0.02$). C_{max} values were lower with the intrarectal ($3.0 \pm 1.0 \text{ mg l}^{-1}$) and intramuscular routes ($3.2 \pm 0.7 \text{ mg l}^{-1}$) than with the intravenous route ($5.1 \pm 1.4 \text{ mg l}^{-1}$) ($P=0.003$). $\text{AUC}(0, 8 \text{ h})$ obtained with the intrarectal ($17.0 \pm 7.4 \text{ mg l}^{-1} \text{ h}$) and intramuscular routes ($19.4 \pm 4.8 \text{ mg l}^{-1} \text{ h}$) were smaller than with the intravenous route ($27.8 \pm 8.2 \text{ mg l}^{-1} \text{ h}$) ($P=0.02$). Bartlett's test did not show any difference in the variability of C_{max} or $\text{AUC}(0, 8 \text{ h})$, but showed that

Figure 2 Mean ($\pm$ s.e. mean) quinine whole blood concentrations-time curves after a) intrarectal administration of 12.8 mg kg^{-1} quinine gluconate (cream formulation) (i.e. 8 mg kg^{-1} quinine base) and b) intramuscular or c) intravenous administration of 8 mg kg^{-1} Quinimax® (i.e. 4.7 mg kg^{-1} quinine base) in children with falciparum malaria. Arrows indicate times of dosing; vertical bars indicate standard errors of the means.

the variability in t_{max} values was higher after intrarectal administration than after the other two routes ($P=0.009$). The approximate bioavailability of quinine by the intrarectal route relative to the intravenous route (extrapolated to the dose of 8 mg kg^{-1} quinine base) was 36% from 0 to 8 h. Approximate bioavailability by the intrarectal route relative to the intramuscular route was 51% from 0 to 8 h.

Discussion

Quinine is the least expensive and most effective treatment for severe malaria in tropical areas where *Plasmodium falciparum* has become resistant to chloro-

Table 2 Pharmacokinetic parameters (mean $\pm$ s.d. and range) of quinine administered by the intrarectal route (quinine gluconate) or by the intramuscular and intravenous routes (Quinimax®) to 21 children with acute uncomplicated falciparum malaria in Niger

	Intrarectal administration (n = 7)	Intramuscular administration (n = 7)	Intravenous administration (n = 7)
$C_{\max}$ (mg l ⁻¹)	3.0 $\pm$ 1.0 2.0–4.8	3.2 $\pm$ 0.7 ⁺⁺ 2.1–4.2	5.1 $\pm$ 1.4 ^{**} 3.5–7.0
$t_{\max}$ [#] (h)	4.0 1.0–8.0	1.2 ^{++*} 0.6–4.0	4.0 3.0–4.2
AUC(0, 8 h) (mg l ⁻¹ h)	17.0 $\pm$ 7.4 9.5–30.0	19.4 $\pm$ 4.8 ⁺ 11.6–27.3	27.8 $\pm$ 8.2 [*] 15.2–39.7

* Significant *vs* intrarectal route (*0.01 < *P* < 0.05), (**0.001 < *P* < 0.01)⁺ Significant *vs* intravenous infusion (⁺0.01 < *P* < 0.05), (⁺⁺0.001 < *P* < 0.01)[#] Median

quine [12]. The intravenous route is the most effective, but is not always suitable for use in the field or even some hospitals, given the need for specific materials and trained staff. In Niger, children account for most cases of *P. falciparum* malaria; they are usually prescribed intramuscular quinine even though the oral form is usually adequate [13], but intramuscular injections can be a source of poliomyelitis, other severe infections, and paralysis of the lower limbs. The oral route is still used effectively in many tropical countries [14, 15], but is unsuitable for comatose and nauseous children. The rectal route is commonly used in paediatric practice (e.g. diazepam) and has been widely assessed as an alternative to parenteral administration [16]. For example, artemisinin suppositories are as effective as intravenous artesunate and quinine for severe malaria [17], and more effective than oral quinine [18, 19]. Rectal administration of non-coated chloroquine tablets for treatment of non-severe malaria in infants in Sierra Leone was successful, and bioavailability was similar to that obtained by the oral route [20]. Unfortunately the suppository formulation is not suitable for hot countries, and quinine bioavailability after administration in suppository form is very irregular. Empirical but satisfactory intrarectal administration of diluted Quinimax® has already been used and has been adopted by many health centres in Madagascar and Niger as an alternative to intramuscular injections [21]. It avoids the complications often associated with intramuscular injections, is easier to use than the intravenous route in the field, is painless, and reduces the risk of infections from already used needles [22].

This study was undertaken to determine whether a new cream formulation of quinine gluconate, specially adapted to the intrarectal route was easy to use, well tolerated, well absorbed and effective. Indeed, the cream formulation is very easy to use as the consistency of the cream greatly facilitated administration, and no expulsion of the product was ever observed, in contrast to the observations with the diluted Quinimax®. It is also well tolerated: in this sample of children, no local irritation was observed with this cream, as already shown in rabbits and healthy volunteers (internal report

from Sanofi), probably because the pH is higher (4.5 instead of 1.9 in standard Quinimax®); the vehicle of the cream, as described above, never induced any diarrhoea. Moreover, in the conditions of our study at Niamey hospital, the intramuscular injections themselves were not associated with abscesses at the injection point, nor with other severe side-effects, often quoted in the field after this route of administration. In any of the three modes of administration used, neither hypoglycaemia nor cardiovascular toxicity was observed, as expected at the dosages used [23]. This cream formulation was not better absorbed than intrarectal diluted Quinimax®, since the approximate bioavailability was about 40% [1]. But, despite this low approximate bioavailability, the inter-individual variability in absorption parameters, $C_{\max}$ and AUC(0, 8 h), was not found to be greater with the intrarectal route than with the other two in this sample of children. In contrast, the interindividual variability in time of absorption ($t_{\max}$) was greater with the intrarectal route suggesting that the variability observed is more due to the anatomical characteristics implied than to the galenic formulation itself. This new galenic formulation seems to be beneficial to the suppository form, for which quinine bioavailability has always been found very irregular both in rate and extent. This cream formulation was as effective as Quinimax® solution administered intramuscularly or intravenously, as reflected by the very similar time course of rectal temperature and parasitaemia in the three treatment groups. These findings are in agreement with the efficacy of intrarectal *vs* intramuscular Quinimax® in Niger, as previously reported by us [1]. These efficacy parameters are actually multifactorial and directly related to the sensitivity of the parasite strains to antimalarial drug, the degree of immunity of infected patients and the disposition of the drug. At the time of the study, all the *P. falciparum* strains were still fully sensitive to quinine in this area of Niger. In children, the antimalarial immunity occurs from about 3 years and potentiates the drug activity. Although the children studied did not differ in age between the three groups, the large range of age in each group can induce differences in degree of immunity and then variability

in efficacy. Despite the relatively low approximate bioavailability of this intrarectal cream, whole blood quinine concentrations were above the minimal inhibitory concentration generally reported in Africa (about 4 mg l^{-1} in plasma, i.e. 3 mg l^{-1} in whole blood) [29]. In parallel, whole blood quinine concentrations after intramuscular and intravenous administration were in good agreement with reported data [12, 23–26], taking into account that whole blood/plasma quinine concentration in malaria children at the beginning of the treatment was found by us to be 0.70 ± 0.14 ($n=7$). These whole blood concentrations led to a similar efficacy of intramuscular quinine to that previously reported by Simao *et al.* [27] and White *et al.* [28] in children with *falciparum* malaria. In our study, the time required to obtain a 50% fall in baseline parasitaemia was similar in the three groups and comparable with values obtained by White *et al.* [28]. Nevertheless, the dosage used of 8 mg kg^{-1} quinine base could be too low for routine treatment of severe malaria in areas with a lower sensitivity level of *P. falciparum*. In a study using progressive doses (8, 13 and 20 mg kg^{-1}) of Quinimax® in children with acute uncomplicated falciparum malaria, we found that the peak concentration and area under the curve of quinine increased linearly with the dose administered, and that the latter could be increased to 20 mg kg^{-1} Quinimax® without increasing side effects and leading to a parasitaemia clearance time of 48 h [30]. Nevertheless, the clinical and parasitological efficacy of this 20 mg kg^{-1} dosage needs to be confirmed by a larger study in children infected with *P. falciparum*. Such a study is now under way by us in Niamey.

In conclusion, the simplicity of use, good tolerability, kinetic properties and efficacy of this new cream formulation of quinine designed for intrarectal administration, suggest that, if confirmed by a larger study with a higher quinine dosage, it might be a safe and effective alternative to intramuscular quinine for the treatment of acute uncomplicated falciparum malaria in children in areas where *P. falciparum* is still sensitive to quinine.

References

- Barennes H, Kahiati F, Pussard E, *et al.* Intrarectal Quinimax for the treatment of *Plasmodium falciparum* malaria in children in Niger: efficacy and pharmacokinetics. *Trans R Soc Trop Med Hyg* 1995; **89**: 418–421.
- Fontoynont, Raharijaona. La poliomyélite antérieure aigüe (paralysie infantile à Madagascar). *Bull Soc Madagascar* 1930; **23**: 554–556.
- Price EW. Inoculation and injection paralysis. *Br Med J* 1950; **2**: 1391–91.
- Sanchetti K. Clinical profiles of 3005 polio children in a rural population. *Ind J Ped* 1979; **46**: 237–244.
- Wyatt HV. Poliomyelitis in developing countries; lower limb in paralysis and injections. *Trans R Soc Trop Med Hyg* 1989; **83**: 545–549.
- Yen LM, Dao LM, Day NPJ, *et al.* Role of quinine in the high mortality of intramuscular injection tetanus. *Lancet* 1994; **ii**: 786–787.
- Scheinberg L, Allensworth M. Sciatic neuropathy in infants related to antibiotic injections. *Pediatrics* 1957; **19**: 261–265.
- Gilles FH, French JH. Post injection sciatic nerve paralysis in infants and children. *J Ped* 1961; **58**: 195–204.
- Guigemde T, Gbary A, Ouedrago JB, *et al.* Points actuels sur la chimiorésistance du paludisme des sujets autochtones dans les états de l'OCCGE (Afrique de l'Ouest). *Ann Soc Belge Méd Trop* 1991; **71**: 199–207.
- Gay F, Diquet B, Katlama C, *et al.* Report of chloroquine resistance malaria in Niger. *Thérapie* 1991; **46**: 89–91.
- Iliadis A, Brown C, Huggins ML. Apis: a software for model identification, simulation and dosage regimens calculation in clinical and experimental pharmacokinetics. *Comp Meth Progr Biomed* 1992; **38**: 227–239.
- White NJ, Looareesuwan S, Warrell DA, Warrell MJ, Bunnag D, Harinasuta T. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *Am J Med* 1982; **73**: 564–572.
- Wyatt HV, Mahadevan S, Srinivasan S. Unnecessary injections and paralytic poliomyelitis in India. *Trans R Soc Trop Med Hyg* 1992; **86**: 546–549.
- Deloron P, Lepers JP, Verdier F, *et al.* Efficacy of a 3-day oral regimen of a quinine quinidine cinchonine association (Quinimax®) for treatment of falciparum malaria in Madagascar. *Trans R Soc Trop Med Hyg* 1989; **83**: 751–754.
- Sowunmi A, Salako A. Evaluation of the relative efficacy of various antimalarial drugs in Nigerian children under five years of age suffering from acute uncomplicated falciparum malaria. *Ann Trop Med Parasitol* 1992; **86**: 1–8.
- Van Hoogdalen EJ, de Boer AG, Breimer DD. Pharmacokinetics of rectal drug administration. Part I. *Clin Pharmacokin* 1991; **21**: 11–26.
- Hien TT, Arnold K, Vinh H, *et al.* Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in treatment of cerebral malaria. *Trans R Soc Trop Med Hyg* 1992; **86**: 582–583.
- Arnold K, Hien TT, Chinh NT, Phu NH, Mai Ph. A randomized comparative study of artemisine (qinghasu) suppositories and oral quinine in acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; **84**: 499–502.
- Hien TT, Tam DTH, Cuc NTK, Arnold K. Comparative effectiveness of artemisin suppositories and oral quinine in children with acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1991; **85**: 210–211.
- Westman L, Kamanda S, Hellgren U, Ericsson Ø, Rombo L. Rectal administration of chloroquine for treatment of children with malaria. *Trans R Soc Trop Med Hyg* 1994; **88**: 446–468.
- Barennes H. Is intra rectal quinine a safe alternative to intra muscular injectable quinine? *Tropical Doctor* 1994; **24**: 32–33.
- Wyatt HV. Injections and AIDS. *Tropical Doctor* 1986; **16**: 97–98.
- White NJ. Antimalarial pharmacokinetics and treatment regimens. *Br J Clin Pharmacol* 1992; **34**: 1–10.
- Shann F, Stace J, Edstein M. Pharmacokinetics of quinine in children. *J Paediat* 1985; **106**: 506–510.
- Stace J, Shann F, Walters S, Conellan M, Edstein M. Serum levels of quinine following intramuscular administration in children. *Papua New Guinea Med J* 1983; **26**: 21–24.
- Waller D, Krishna S, Craddock C, *et al.* The pharmacokinetic properties of intramuscular quinine in Gambian children with severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; **84**: 488–491.
- Simão F, Macome A, Pateguana F, Schapira A. Comparison of intramuscular sulfadoxine-pyrimethamine and intramuscular quinine for the treatment of falciparum

- malaria in children. *Trans R Soc Trop Med Hyg* 1991; **85**: 341–344.
- 28 White NJ, Waller D, Kwiatkowski D, Krishna S, Craddock C, Brewster D. Open comparison of intramuscular chloroquine and quinine in children with severe chloroquine sensitive falciparum malaria. *Lancet* 1989; **ii**: 1313–1316.
- 29 White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokin* 1985; **10**: 167–215.
- 30 Barennes H, Mahaman Sani A, Pussard E, *et al.* Intrarectal Quinimax[®] (a combination of Cinchona alkaloids) administered at three different dosages to children with *Plasmodium falciparum* malaria in Niger. *Clin Drug Invest* 1996; **11**: (in press).

(Received 27 June 1995,
accepted 22 November 1995)