A single dose of intramuscular sulfadoxine-pyrimethamine as an adjunct to quinine in the treatment of severe malaria: pharmacokinetics and efficacy

C. R. J. C. Newton[1,2], P. A. Winstanley[1,3], W. M. Watkins[1,3], I. N. Mwangi[1], C. M. Waruiru[1], E. K. Mberu[1], P. A. Warn[1,4], C. G. Nevill[5] and K. Marsh[1,4] [1]*Kenya Medical Research Institute, Kilifi Research Unit, Kilifi, Kenya;* [2]*Department of Paediatrics, University of Oxford, Oxford, UK;* [3]*Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK;* [4]*Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK;* [5]*Malaria Unit, African Medical Research Foundation, Nairobi, Kenya*

Abstract

It has been suggested that sulfadoxine-pyrimethamine (SD/PM) may be useful in the treatment of severe malaria since it could enhance the killing of parasites by quinine (QN) and it can be given as a single intramuscular injection. Eighty Kenyan children with severe malaria were allocated at random to receive either intramuscular QN alone (quinine dihydrochloride 20 mg salt/kg as a loading dose, followed by 10 mg salt/kg 12 hourly for a total of 6 doses) or the same QN regimen plus one intramuscular injection of SD/PM (sulfadoxine 25 mg/kg, pyrimethamine 1·25 mg/kg). There was no difference in time to defervescence, aparasitaemia, or 50% reduction in parasitaemia, parasite elimination half-life, or mortality between the 2 groups. In addition, the concentrations of SD and PM were measured in 14 children and of QN in 8 of these children. Concentrations needed to achieve synergy against PM-resistant strains of *Plasmodium falciparum* were achieved in all of the children with severe malaria within the first hour and maintained for more than 72 h. SD/PM did not perturb the pharmacokinetics of QN.

Introduction

Most African children who receive treatment for severe malaria do so in rural hospitals. Since these centres often lack the staff and facilities for the safe administration of the recommended intravenous regimen of quinine (QN), the possible role of other antimalarials in these children needs to be investigated. The parenteral formulation of sulfadoxine-pyrimethamine (SD/PM) has two potential roles in the treatment of severe malaria. Firstly, because it preferentially acts at a later stage in the parasite cycle than does QN (RIECKMAN *et al.*, 1987; WHITE & KRISHNA, 1989), the combination of the 2 drugs may be expected to kill a greater proportion of the parasites in the critical first 24–48 h of therapy. Secondly, although not recommended for the sole therapy of severe malaria (WARRELL *et al.*, 1990), the simplicity of a single intramuscular injection of SD/PM may have considerable advantages when QN is either not available or cannot be used safely. In these circumstances the recommendation for appropriate regimens is made difficult by the absence of any pharmacokinetic data from patients with severe malaria.

We have conducted an open randomized trial of parenteral SD/PM as an adjunct to QN for the treatment of severe falciparum malaria in Kenyan children using clinical progress and rate of parasite clearance as outcomes. Furthermore, since SD/PM may be used alone for the treatment of severe malaria under some circumstances, we examined the pharmacokinetics of this combination in this group of children under the cover of QN.

Materials and Methods

Eighty children with acute falciparum malaria, admitted to Kilifi District Hospital, Kenya, were studied if they had one or more of the following criteria for severe malaria: (i) cerebral malaria (WARRELL *et al.*, 1990); (ii) prostration—i.e., unable to sit unsupported or drink; (iii) severe anaemia (haemoglobin <50 g/L) with a parasitaemia greater than 300 000 per mm^3; (iv) parasitaemia greater than 600 000 per mm^3.

The patients were allocated at random in pairs to receive either intramuscular (i.m.) QN alone or the same regimen plus i.m. SD/PM. The QN regimen comprised a loading dose (quinine dihydrochloride, Paris Chemicals; 20 mg salt/kg) followed by maintenance doses every 12 h (10 mg salt/kg) to a total of 6 doses. The maintenance doses were given parenterally until the child could drink and thereafter quinine sulphate (prepared extemporaneously as a syrup) was administered. All QN injections were diluted 1:5 in water for injection; loading doses were given by deep i.m. injection, half into each anterior thigh, while maintenance doses were given into alternate thighs. SD/PM (Fansidar® parenteral, Hoffmann La Roche; 1·25 mg/kg PM and 25 mg/kg SD) was given as a single i.m. injection at the same time as the QN loading dose.

The children were assessed every 6 h and temperatures were measured with a mercury thermometer, usually per rectum. Thick and thin blood films were prepared every 6 h during the first 72 h of therapy and every 12 h thereafter. The blood films were stained with Giemsa's stain and the parasitaemia was counted against 100 nucleated cells or as a percentage of 500 red blood cells if there were more than 1000 parasites per 100 nucleated cells. The calculation of parasitaemia was based upon concomitant nucleated cell or red cell counts and expressed as counts per mm^3.

Sampling

Blood for measurement of PM and SD (1·0 ml) was drawn, using an indwelling intravenous cannula until discharge and by venepuncture thereafter, before treatment and at the following times after dosing: 1, 2, 4, 6, 12, 24, 48, 72 and 96 h. Samples for QN (200 µl) were drawn before treatment began and at the following times: 1, 2, 4, 6 and 12 h. After 96 h most children had been discharged; later blood samples were therefore taken at unregulated times, when children were presented for follow-up.

Measurement of pyrimethamine, sulfadoxine and quinine

Blood was taken into lithium heparin tubes; two 100 µl aliquots were transferred to filter paper strips for QN measurement, the remainder was centrifuged (ca 1000 *g*; 5 min) within 8 h of sampling and the plasma was transferred to filter paper strips (50 µl×2 for measurement of SD, and 200 µl×2 for PM). The paper strips were dried and stored at room temperature out of direct sunlight. QN concentrations were measured in Nairobi by the high performance liquid chromatography (HPLC) method (MBERU *et al.*, 1991). PM and SD were measured by the HPLC methods of WINSTANLEY *et al.* (1992). In the PM assay a large peak with the same retention time (t_r) as QN (2·5 min) was followed by PM (t_r=5·5 min). The 3 peaks were resolved to within 10% of baseline. To determine whether measurement of PM was perturbed, QN (15 µg/ml) was added to all PM calibration samples which were compared with QN-free samples.

Address for correspondence: Dr C. R. J. C. Newton, Kilifi Research Unit, P.O. Box 428, Kilifi, Kenya.

Calculations

Pharmacokinetic characteristics were calculated using standard formulae (ROWLAND & TOZER, 1989). When the concentration of PM and SD was measured at one or more time points after 168 h, but not at 168 h, the concentration at this point was calculated by log-linear regression analysis of post-absorption and distribution phase data.

Time to aparasitaemia was taken as the difference between the start of antimalarial therapy and the first of 2 consecutive negative blood slides (assessed against 300 nucleated cells); time to defervescence was taken to be the first of 2 consecutive temperatures <37·5°C. Parasite counts were plotted semi-logarithmically against time. Time to 50% parasitaemia was determined by inspection and was recorded only if the starting parasitaemia was greater than 10 000 per mm^3 and the drop to 50% parasitaemia was assessed by blood slides every 6 h. The slope of the log-linear phase was calculated by regression analysis using all points between, and including, maximum parasitaemia and the last available data point. Where the correlation coefficient was significant at the 5% level, or better, the slope of the line was recorded, and the parasite elimination rate constant, k_{para}, was calculated from 2·303×slope; the parasite elimination half time ($t_{1/2para}$) was calculated from $0{\cdot}693/k_{para}$. A sample size of 25 values in each treatment group was needed to detect a difference of 2 h in $t_{1/2para}$ at the 5% level.

Both clinical and parasitological endpoints were compared using Student's *t* test. Comparisons between pharmacokinetic data from the present study and those of WINSTANLEY *et al.* (1992) were made by the Mann-Whitney *U* test.

The study was approved by the ethical committee of the Kenya Medical Research Institute.

Results

On admission, there was no significant difference between the 2 groups of children (Table 1). There was no significant difference in the time to defervescence, the number of children requiring blood transfusions, or mortality between the 2 groups (Table 2). Similarly, the rates of parasite clearance did not differ significantly.

Table 1. Admission characteristics of children with severe malaria

	Quinine alone	Quinine+ sulfadoxine/ pyrimethamine
Number	40	40
Age (months)[a]	39·1±22·16	33·1±19·65
Criteria for severity		
Cerebral	15	15
Prostrate	18	15
Anaemia	3	8
Hyperparasitaemia	4	2
Duration of fever (d)[a]	3·6± 2·11	4·0± 4·53
Temperature (°C)[a]	39·2± 9·57	39·0± 1·150
Parasitaemia (per mm^3)		
<60 000	13	15
60–600 000	15	14
>600 000	12	11
Haemoglobin (g/L)[a]	71·4±24·64	68·8±24·01
Hypoglycaemia (blood glucose <2·2 mmol/L)	4	2

[a]Mean±standard deviation.

The disposition of SD/PM was studied in 14 children given QN plus SD/PM (6 females, 8 males; age range 8–84 months), and that of QN in 8 of these (7 with cerebral malaria and 7 who were prostrate). Admission laboratory test values were as follows: parasitaemia 75–1 757 700 (geometric mean 73 961) per mm^3; haemoglobin 70±17 g/L (mean±standard deviation); glucose 4·5±1·0 mmol/L (3 patients were hypoglycaemic on admission). QN concentrations were also measured during the first dose interval (0–12 h) in 15 children given QN alone.

Table 2. Outcome of the two treatment regimes for malaria

	Quinine alone	Quinine+ sulfadoxine/ pyrimethamine
Deaths	3	2
Transfusions	11	13
Time to defervescence[a]	25·1±16·00 (28)	20·1±18·86 (29)
Time to aparasitaemia[a]	49·5±15·22 (33)	45·9±14·61 (34)
Time to 50% reduction in parasitaemia[a]	12·1± 9·03 (34)	14·2± 9·58 (34)
Parasite elimination half time	4·5± 2·2 (26)	4·2± 2·7 (29)

[a]Mean±standard deviation (number of subjects in parentheses).

Fig. 1 shows the mean concentration versus time profiles for QN, SD and PM in those children given QN plus SD/PM. The derived pharmacokinetic parameters are given in Table 3; there was no significant difference in these values between the children with cerebral malaria and those with the other criteria of severe malaria.

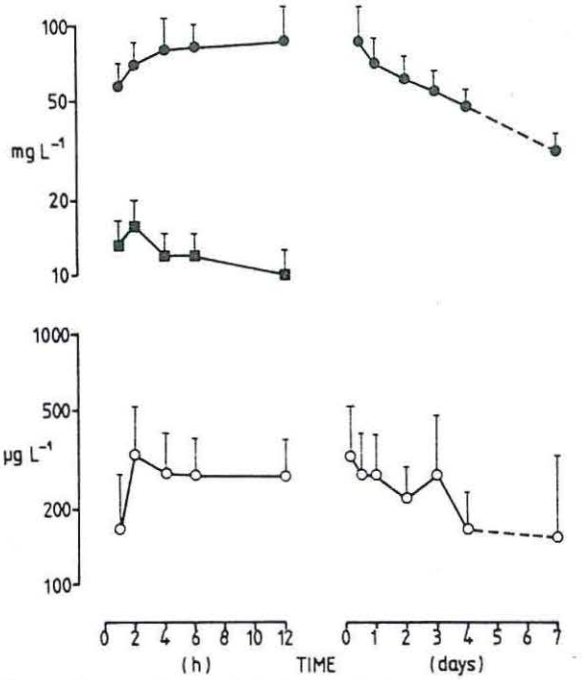

Figure. Means and standard deviations of plasma concentrations of sulfadoxine (●) in 14 children, pyrimethamine (○) in 11 children, and whole blood concentrations of quinine (■) in 8 children.

The mean maximum plasma concentrations (C_{max}) and area under the concentration vs. time curve extrapolated to infinity (AUC) for SD in the present study (89·8 mg/L and 15,927 mg/L/h respectively) were lower than in children with non-severe malaria (WINSTANLEY *et al.*, 1992) given i.m. SD/PM (114·9 mg/L [P=0·024] and 24 253 mg/L/h [P=0·006] respectively). However, time to maximum concentration (t_{max}) and elimination halftime ($t_{1/2}$) for SD in the present study were not significantly different from those in non-severe malaria. PM was absorbed faster in the present study than in non-severe malaria (t_{max} 19·8 vs. 41·1 h; P=0·028], and mean C_{max} in the present study (449 μg/L) was significantly higher than in non-severe malaria (288 μg/L; P=0·021). Although the AUC vs. time curve of PM for the first 24 h after dosing (AUC_{0-24}) was higher in the present study (6549 μg/L/h) than in non-severe malaria (3898 μg/L/h), the difference was not significant (P=0·065). It was not possible to calculate AUC or $t_{1/2}$ values for PM.

Whole blood QN concentrations 2 h after dosing and AUC_{0-12} were 15·9±4·4 mg/L and 147±35 mg/L/h re-

Table 3. Pharmacokinetic characteristics of pyrimethamine and sulfadoxine

No.	Sulfadoxine C_{max} (mg/L)	t_{max} (h)	$AUC_{0-\infty}$ (mg/L/h)	$t_{1/2}$ (h)
14	89·8±25·8	9·1±7·0	15,927±1,808	134±29
	Pyrimethamine			
No.	C_{max} (μg/L)	t_{max} (h)	AUC_{0-24} (μg/L/h)	
11	449±157	19·8±27·6	6,549±2,356	

[a] C_{max} = mean maximum plasma concentration, t_{max} = time to maximum plasma concentration, $AUC_{0-\infty}$ = area under the concentration vs. time curve extrapolated to infinity, means ± standard deviations. AUC_{0-24} = area under the concentration vs. time curve for the first 24 h after dosing; means ± standard deviations.

spectively in children given QN plus SD/PM, and 13·5±2·8 mg/L ($P>0·05$) and 135±24 mg/L/h ($P>0·05$) respectively in those given QN alone.

None of the children had significant induration (>5 mm) at the sites of the injection and no skin rash or agranulocytosis was documented.

Discussion

The combination of SD and PM remains an effective antimalarial throughout sub-Saharan Africa, though it has not been recommended as the sole agent for the treatment of severe malaria because of its reputed slowness in killing parasites and concern about the development of resistance. However, there has been a resurgence of interest in the use of SD/PM in complicated malaria, since the delay in action has been challenged recently and the expected rapid advance of resistance has not occurred. We have shown that SD and PM are adequately absorbed within the first hour after a single i.m. injection in children with severe malaria and the concentrations needed to achieve synergy against PM-resistant strains of *Plasmodium falciparum* (CHULAY *et al.*, 1984) were maintained for more than 72 h. However, the addition of SD/PM to QN at the start of therapy did not improve the clinical outcome or parasite clearance in these children.

SD/PM has been shown to work as quickly as QN. In 2 randomized trials comparing QN and SD/PM in children with non-severe malaria, there was no significant difference in time to defervescence or parasite clearance when the drugs were administered orally (NEVILL & WATKINS, 1990) or intramuscularly (SIMAO *et al.*, 1991). Furthermore, reinterpretation of the data on which the combination's slowness of action was based and other hitherto unpublished data from south-east Asia support these findings (WATT & SHANKS, 1991). Although isolated cases of SD/PM resistance in non-immune subjects were reported 10 years ago from East Africa (MARKWALDER & MEYER, 1982; NGUYEN-DINH *et al.*, 1982), and SD/PM does not completely clear parasites in a proportion of semi-immune children (SPENCER *et al.*, 1984; KILIMALI & MKUFYA, 1985), recent reports from West Africa (LEGE-OGUNTOYE *et al.*, 1990; SALAKO *et al.*, 1991) and East Africa (HELLGREN *et al.*, 1990) suggest that SD/PM resistance is sporadic and spreading slowly. Therefore the arguments against the use of SD/PM in severe disease are not so clear-cut; certainly its use as a single i.m. injection has significant advantages. However, one concern is the total absence of any pharmacokinetic data on its use in severe malaria; hence we chose to study this under the cover of simultaneous therapy with QN.

The disposition of PM and SD differed from that seen in non-severe malaria (WINSTANLEY *et al.*, 1992). PM concentrations in the present study were higher in the first 24 h and t_{max} was shorter. These observations probably reflect an increased rate of absorption of PM in children with severe malaria. The explanation of faster absorption of this poorly water-soluble base is unknown, but changes in muscle blood flow and tissue pH could play a part. In the case of SD, C_{max} and $AUC_{0-\infty}$ values were lower than in non-severe malaria, but $t_{1/2}$ was unchanged, which suggests disease-induced increases in apparent volume of distribution and clearance. Apart from the dissimilarity in disease severity, one obvious difference between the 2 studies was the concomitant administration of QN to our patients. QN concentrations were similar to those reported when the drug was used alone in children with severe malaria (PASVOL *et al.*, 1991). It seems unlikely, however, that the observed difference in the disposition of PM or SD can be explained by interaction with QN. QN is an inhibitor of hepatic mixed function oxidases (RIVIERE & BACK, 1986) and might be expected to reduce the clearance of PM while having little effect on SD (BOHNI *et al.*, 1969).

The second question of interest was whether the addition of a drug acting on the more mature stages of the parasite would give any clinical advantage. SD/PM is often given at the end of a course of QN to help eradicate the parasites in severe malaria (HALL *et al.*, 1975), which is too late for the extra benefit of its anti-schizontocidal activity. In a previous study the addition of SD/PM to QN at the start of treatment was associated with shorter duration of fever and parasitaemia in non-immune American soldiers (BARTONELLI *et al.*, 1967). However, in a randomized trial of QN alone versus QN plus a dose of SD/PM in 52 patients with cerebral malaria, no difference was detected in mortality or duration of therapy (NAPARSTEK *et al.*, 1981). We observed no benefit in terms of clinical response or parasite clearance, though this cannot be taken to exclude the possibility of a small positive effect, as such studies would require very large numbers of patients with mortality as the outcome.

In children with severe malaria, SD/PM does not appear to be a useful adjunct to QN, except to enhance eradication. Concerns about drug resistance and the lack of data on the combination's efficacy when used alone in severe malaria militate against the recommendation for its use as an alternative to QN at present. However, its good pharmacokinetic profile in severe disease and efficacy in non-severe disease indicated that it may be an alternative first-line therapy in circumstances where QN is not available or cannot be used safely.

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Announcement

British Society for Parasitology
5th Malaria Meeting
23–24 September 1993
Institute for Molecular Medicine, John Radcliffe Hospital, Oxford, UK
Workshops on MDR and Transfection on 22 September 1993

Invited speakers include: Peter David (Paris); Adrian Hill (Oxford); Kevin Marsh (Kilifi/Oxford); Andrew McMichael (Oxford); Kathryn Robson (Oxford); Andrew Slater (NY) and Bill Watkins (Nairobi).
A conference dinner will be held at Keble College, Oxford.
Enquiries: Dr Christine Facer, Malaria Laboratory, Department of Haematology, The London Hospital Medical College, Turner Street, London, E1 2AD, UK. Tel: 071 377 7618 (direct); Fax: 071 377 7677.