Fever in uncomplicated *Plasmodium falciparum* malaria: randomized double-'blind' comparison of ibuprofen and paracetamol treatment

S. Krishna[1,2*], **S. Pukrittayakamee**[1], **W. Supanaranond**[1], **F. ter Kuile**[1], **M. Ruprah**[3], **T. Sura**[4] and **N. J. White**[1,2]
[1]*Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand;* [2]*Centre for Tropical Diseases, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, OX3 9DU, UK;* [3]*Poisons Unit, Avonley Road, London, SE14 5ER, UK;* [4]*Department of Medicine, Ramathipodi Hospital, Rama 6 Road, Bangkok 10400, Thailand*

Abstract

Fever almost invariably accompanies uncomplicated falciparum malaria. In a randomized, double-'blind' study, we compared a single dose of ibuprofen (10 mg/kg, $n=8$) with paracetamol (15 mg/kg, $n=8$) for the treatment of fever >38·5°C due to uncomplicated falciparum malaria. Ibuprofen was significantly more effective than paracetamol in lowering temperatures throughout the first 4·5 h after dosing ($P=0·016$) and should be considered as an antipyretic agent in the management of uncomplicated falciparum infections, providing there is no contraindication to its use.

Keywords: malaria, *Plasmodium falciparum*, antipyrexia, ibuprofen, paracetamol

Introduction

We have recently shown that quinine alone was ineffective as an antipyretic agent in uncomplicated falciparum malaria, whereas paracetamol rapidly lowered temperatures and improved symptoms associated with fever in malaria (KRISHNA *et al.*, 1995). Ibuprofen, the safest of the non-steroidal anti-inflammatory drugs (NSAIDs) (LANGMAN *et al.*, 1994; RODRIGUEZ & JICK, 1994), has been shown in some comparative trials to produce a more rapid, larger, and more sustained fall in fever than paracetamol (reviewed by MACKOWIAK, 1991). However, any antipyretic advantage of ibuprofen must be weighed against an increased potential for adverse effects. The purpose of this trial was to compare the antipyretic efficacy and tolerance of ibuprofen and paracetamol in adult febrile patients with uncomplicated falciparum malaria.

Methods

Patients

This was a randomized, double 'blind' comparison of a single dose of ibuprofen or paracetamol in the treatment of malarial fever in non-pregnant adults. Patients were enrolled into the study providing they had uncomplicated falciparum malaria (WHO, 1990), an oral temperature >38·5°C, and gave informed consent. Patients were excluded if they had contraindications to the use of paracetamol or ibuprofen (specifically a history of asthma, dyspeptic symptoms, gastro-intestinal bleeding, or allergy to ibuprofen), or gave a history of antipyretic or antimalarial drug use within 6 h of presentation. The study was approved by the Ethical Clearance Committee of the Faculty of Medicine, Ramathipodi Hospital, Bangkok, Thailand.

Procedures

Randomization and administration of antipyretic medication was carried out by an individual otherwise unconnected with the study. The physicians responsible for patient care and for monitoring antipyretic responses remained unaware of the patients' antipyretic treatments until the study had been completed. After a full history and examination the patient was weighed and blood was sampled for biochemical and haematological indices, parasitaemia and drug assay (paracetamol and ibuprofen). Thereafter plasma was sampled at 2 and 5 h after admission for determination of antipyretic drug levels.

On admission, all patients received oral quinine sulphate (10mg salt/kg; Government Pharmaceutical Organization, Bangkok, Thailand). Patients were then allocated at random to receive either paracetamol elixir (15 mg/kg in a 50 mg/mL suspension; Calpol®, Wellcome Foundation, UK) or ibuprofen suspension (10 mg/kg in a 20 mg/mL suspension; Junifen®, kindly supplied by Boots Pharmaceuticals, UK).

Symptoms of headache, myalgia, nausea, vomiting and sweating were recorded on a standard form every half hour during the 8 h study period. Oral temperatures, measured with a standard mercury thermometer, were recorded twice at each half hour and remeasured if the 2 readings differed >0·1°C. Patients were monitored for parasitological responses to treatment in the standard way (WHITE & KRISHNA, 1989). Tetracycline (250 mg every 6 h) was added to quinine to complete a 7 d course of both drugs.

Drug assay

The paracetamol assay has been described previously (KRISHNA *et al.*, 1995). Ibuprofen levels were measured in duplicate on plasma samples (or standards of 5, 10, 20, 30, 40 mg/L in porcine plasma) after mixing with acetonitrile (100 µL, 1:1 v/v) containing benoxaprofen (5 mg/L) as an internal standard. The mixture was vortexed and centrifuged (9950*g*, 2 min) and 130µL were injected on to a high performance liquid chromatography (HPLC; Hypersil 5 ODS) system. The detection wavelength was 220 nm. The inter- and intra-assay coefficients of variation between 0·7 and 45·8 mg/L were <5%.

Statistical analysis

Mean data are presented with standard deviations in parentheses. Analysis of baseline variables was with ANOVA® after normalization of distributions if appropriate. Measures repeated over time were analysed with univariate and multivariate repeat measures analysis in SYSTAT® (version 5·2, Evanston Inc., USA) with two-tailed values of $P<0·05$ indicating significant differences. Repeat measures analysis was restricted to time series <7·5 h and one missing value was substituted with a group mean.

Results

Clinical features

Sixteen patients entered the study, 8 in each treatment group. All presented with histories of fever, 15 (94%) with headache, 11 (70%) with nausea, 8 (50%) with vomiting and 7 (44%) with generalized myalgias. The baseline clinical variables of these patients were comparable for demographic characteristics (age and sex), vital signs (pulse, blood pressure, respiration), and laboratory investigations (plasma lactate, albumin, blood urea nitrogen) (data not shown). Geometric mean parasitaemia and mean oral temperature were respectively 31 250

*Current address for correspondence: Division of Infectious Diseases, Department of Cellular and Molecular Sciences, St George's Hospital Medical School, Cranmer Terrace, London, SW17 0RE, UK.

(range 8600–117 400)/μL and 39·5(0·7)°C in ibuprofen recipients, and 26 400(40–400 000)/μL and 40(0·6)°C in paracetamol recipients.

Temperature responses to ibuprofen and paracetamol

The mean temperature responses in the 2 treatment groups during the 8 h study are shown in the Figure.

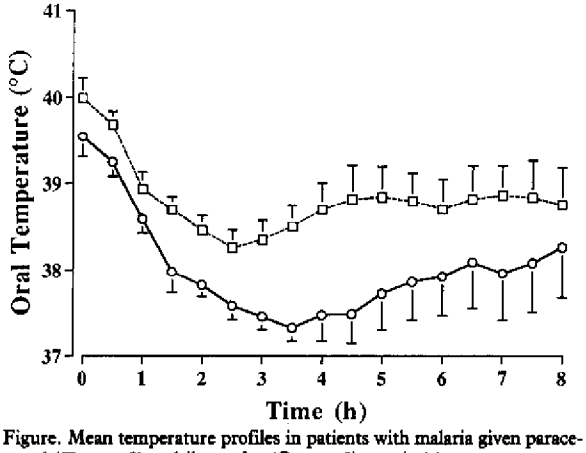

Figure. Mean temperature profiles in patients with malaria given paracetamol (□, n = 8) and ibuprofen (○, n = 8); vertical bars represent one standard error of the mean.

The mean starting temperatures (39·5(0·66)°C in the ibuprofen recipients and 40(0·6)°C in the paracetamol recipients) were not significantly different. The mean temperature nadir was significantly lower in the ibuprofen group than in the paracetamol group (36·9(0·7)°C and 37·9(0·7)°C, $P<0·01$). Initial temperatures were not related to the maximum observed falls. The differences in temperature responses in the 2 groups were significantly different by repeat measures analysis for 4·5 h after admission (Wilks's ΛF statistic=8·1, $P=0·016$). To allow for differences in admission temperature, the changes in temperature from baseline were compared; the reduction in fever by ibuprofen was significantly greater than that associated with paracetamol at 3 h (Wilks's ΛF statistic=8, $P=0·0028$) and 4 h (Wilks's ΛF statistic=4·8, $P=0·021$). The mean time to lowest temperature (from inspection of individual profiles) in ibuprofen recipients was 4·6(2·2) h and in paracetamol-treated patients it was 3·9(2·5) h ($P>0·5$).

Plasma concentrations

No patient had a detectable paracetamol or ibuprofen plasma level at the start of the study. Mean paracetamol levels measured 2 and 5 h after the administration of quinine tablets were 6·9(4) mg/L and 2·3(2·9) mg/L respectively. Mean ibuprofen levels at 2 and 5 h after admission were 12·2(5·5) and 6(2·7) mg/L respectively. There was no relationship between drug levels measured at 2 h and measures of efficacy such as the time to, and the magnitude of, the maximum fall in temperature in this small study.

Clinical responses and toxicity

Sweating began 0·5–1 h after the antipyretic had been taken. Headache responded to ibuprofen over a more sustained period than paracetamol (all patients were headache free for 1·5 h with ibuprofen, whereas paracetamol did not abolish headache in all patients, and the frequency of headache increased again after 1 h of symptomatic improvement). With both antipyretic agents, the nadir in symptoms corresponded to the nadir in temperature. With paracetamol this was usually at 2·5–3 h and for ibuprofen 3·5 h (not shown). Two or 3 h after ibuprofen, one patient had marked worsening of an urticarial eruption on his upper trunk which had been present on admission. This rash responded to intramuscular chloropheniramine (10 mg). One paracetamol recipient had abdominal pain and watery diarrhoea which settled without specific therapy. There was no relationship between admission temperature and measures of parasite or fever clearance.

Discussion

The transient elevation in circulating pro-inflammatory cytokines provoked by pyrogens from infected erythrocytes resets the hypothalamic thermostat to a higher level and causes fever in malaria (KWIATKOWSKI, 1990). These cytokines also produce the constitutional symptoms of uncomplicated falciparum malaria including malaise, headache, nausea and vomiting, and myalgias. Similar processes are responsible for fever in vivax malaria (KARUNAWEERA *et al.*, 1992; MENDIS, 1992). In patients with uncomplicated malaria, quinine effectively treats the underlying cause of fever in hours or days but has no direct effect on fever (KRISHNA *et al.*, 1995). The choice of a cheap and effective antipyretic agent is therefore important in the management of uncomplicated malaria. Ibuprofen is both widely used and safe and only slightly more expensive than paracetamol.

Physicians have been wary of prescribing NSAIDs for fear of increasing the frequency of gastro-intestinal bleeding. However, there is considerable variation in the capacity to cause side-effects within the NSAID group, and these are often dose-related and associated with prolonged use. Ibuprofen has emerged as the safest representative of this class of drug. It has been given to over 250 million children with fever for symptomatic relief (ANONYMOUS, 1991), and 2 recent studies have confirmed that ibuprofen is the least likely NSAID to induce gastro-intestinal bleeding (LANGMAN *et al.*, 1994; RODRIGUEZ & JICK, 1994).

This study was therefore designed to test the hypothesis that ibuprofen is better than paracetamol for the management of fever in uncomplicated malaria. Although the speed of onset of antipyretic effect was similar, temperature reduction following ibuprofen was larger and more sustained than that following paracetamol. This temperature response was also mirrored in the symptomatic improvement reported by patients. The benefit with both antipyretics was evident for 2–4 h. After this time, fever and other symptoms began to return. This study was not designed to determine the optimal dosing frequency of either antipyretic, but it seems likely that paracetamol needs to be given more frequently than ibuprofen (and perhaps in increased dosage) to produce comparable pharmacodynamic effects. The results of this preliminary study refer to 'standard' dosing with the 2 drugs. Whether higher doses of paracetamol would be more effective, and if similar results obtain in children, must await further investigation. The results of this study should not be generalized to the management of severe malaria, when ibuprofen cannot be recommended as an antipyretic. The overriding priority in the management of severe malaria is to save life, whereas symptomatic relief is one of the main objectives in the management of uncomplicated malarial infection. Ibuprofen is better than paracetamol in achieving this objective.

Acknowledgements

We are grateful to Khun Silamut and Ms Estée Török for technical assistance. This study was part of the Wellcome–Mahidol Oxford University Collaborative Tropical Research Programme. S. K. is a Wellcome Trust Senior Research Fellow in Clinical Science.

References

Anonymous (1991). Management of childhood fever. *Lancet*, **338**, 1049–1050.

Karunaweera, N. D., Grau, G. E., Gamage, P., Carter, R. & Mendis, K. N. (1992). Dynamics of fever and serum levels of tumour necrosis factor are closely associated during clinical paroxysms in *Plasmodium vivax* malaria. *Proceedings of the National Academy of Sciences of the USA*, **89**, 3200–3202.

Krishna, S., Supanaranond, W., Pukrittayakamee, S., ter Kuile, F., Supputamangkol, Y., Attatamsoonthorn, K., Ruprah, M. & White, N. J. (1995). Fever in uncomplicated *Plasmodium falciparum* infection: effects of quinine and paracetamol. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **89**, 197–199.
Kwiatkowski, D. (1990). Tumour necrosis factor, fever and fatality in falciparum malaria. *Immunology Letters*, 25, 213–216.
Langman, M. J. S., Well, J., Wainright, P., Lawson, D. H., Rawlins, M. D., Logan, R. F. A., Murphy, M., Vessey, M. P. & Colin-Jones, D. G. (1994). Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet*, **343**, 1075–1078.
Mackowiak, P. A. (1991). *Fever. Basic Mechanisms and Management*. New York: Raven Press.
Mendis, K. (1992). Contrasting clinical disease in *Plasmodium vivax* and *Plasmodium falciparum* malaria, and the association of both with cytokines. *Bulletin de l'Institut Pasteur*, **90**, 3–9.
Rodriguez, L. A. G. & Jick, H. (1994). Risk of associated upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet*, **343**, 769–772.
White, N. J. & Krishna, S. (1989). Treatment of malaria: some considerations and limitations of the current methods of assessment. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **83**, 767–777.
WHO (1990). Severe and complicated malaria, 2nd edition. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **84**, supplement 2.

Received 7 March 1995; revised 21 April 1995; accepted for publication 25 April 1995

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1995) **89**, 509–510

Short Report

Multiple invasion of red blood cells by *Plasmodium vivax in vivo*

Jean Poirriez[1], **Georges Snounou**[3] and **Dominique Blanckaert**[2] [1]*Laboratoire de Biologie and* [2]*Service de Pédiatrie, Centre Hospitalier, 130 Avenue Louis Herbeaux, B. P. 6367, 59385 Dunkerque Cédex 1, France;* [3]*St Mary's Hospital Medical School, Imperial College of Science, Technology and Medicine, Department of Infection and Tropical Medicine, Lister Unit, Northwick Park Hospital, Harrow, Middlesex, HA1 3UJ, UK*

Keywords: malaria, *Plasmodium vivax*, multiple infection of erythrocytes

Plasmodium vivax, which preferentially invades reticulocytes, generally produces low parasitaemias. Multiple infection of red blood cells by *P. vivax* is considered rare. We present a case of *P. vivax* infection, confirmed by the polymerase chain reaction (PCR), in which numerous multiply infected red cells were observed. This, and other similar cases reported by us and others (reviewed by POIRRIEZ *et al.*, 1991; WITZIG & BARKER, 1994), suggest that multiple infections by *P. vivax* may be more common than previously perceived.

A 2 years old boy was admitted in July 1994 to the Centre Hospitalier Général de Dunkerque, France, with a week's history of high fever, convulsions, otitis, and slight enlargement of the spleen. Six months previously he had returned from a 2 months' visit to the Comoro Islands, during which time he was taking antimalarial prophylaxis (chloroquine 25 mg/d) irregularly. His older brother had been treated for falciparum malaria 15 d after returning from that trip. On admission, a full blood count showed haemoglobin 10·5 g/dL, and the blood film showed microcytosis and hypochromia. The platelet count was 72 × 10^9/L, and the reticulocyte count was 1·1%. Giemsa-stained thin blood films revealed *P. vivax* with a high parasitaemia (24 700 infected cells/μL or 0·5% of total red blood cells). The patient was treated with intravenous quinine perfusion (100 mg, 3 times a day) for 5 d. He then received chloroquine (25 mg/d) for 2 months. His condition improved, and no further instance of fever was recorded.

Only *P. vivax* was observed microscopically on the thin blood films, and 24·2% of the invaded red cells were

Table. Distribution of *P. vivax* parasites in 1000 infected red blood cells

No. of parasites per cell	No. of infected cells	No. of blood cells infected with different numbers of each parasite stage[a]				
		T	S	G	T+G	S+G
1	758	553	84	121	–	–
2	179	147	6	2	15	9
3	48	42	1	–	4[b]	1[c]
4	12	12	–	–	–	–
5	3	3	–	–	–	–
Total	1000	757	91	123	19	10

[a]T=trophozoite, S=schizont, G=gametocyte; T+G and S+G indicate simultaneous infection with a sexual and an asexual parasite.
[b]Two trophozoites with one gametocyte in the same red cell.
[c]Two schizonts with one gametocyte in the same red cell.

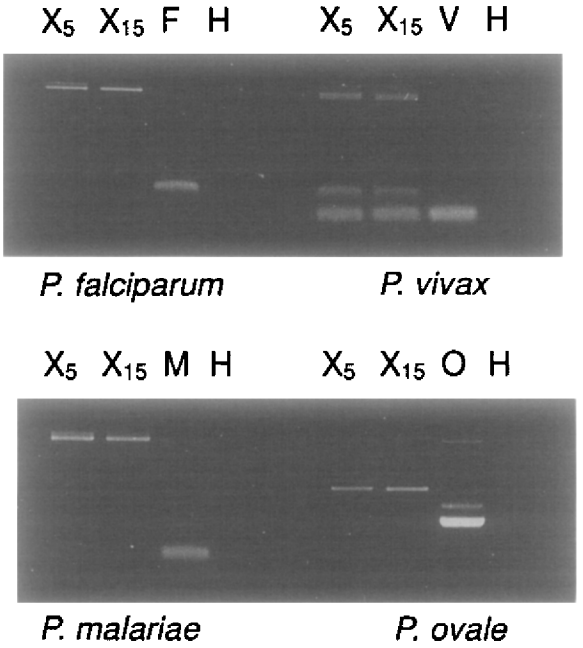

Figure. Determination of the parasite species by PCR analysis of the DNA isolated from 5 μL and 15 μL of blood samples (X_5 and X_{15} respectively) obtained from the patient. Positive controls were genomic DNA isolated from *P. falciparum* (F), *P. vivax* (V), *P. malariae* (M) and *P. ovale* (O), with human genomic DNA (H) being used as a negative control. The nested PCR assay has been described in detail elsewhere (SNOUNOU *et al.*, 1993). Briefly, the bands of higher molecular weight represent the product of the first PCR, in which genus-specific primers are used. In the second PCR species-specific primers are used and the diagnostic PCR product (205, 120, 144, and *c.* 800 base pairs respectively for the 4 species listed) is the lowest band observed in the positive control lanes. In the *P. vivax* panel, the extra band migrating immediately above the diagnostic band (lanes X_5 and X_{15}) indicates the presence of high quantities of parasite DNA. The samples in the *P. ovale* panel were electrophoresed approximately twice as long as the other samples, thus the bands observed in the X_5 and X_{15} lanes correspond to the product of the first PCR reaction. Electrophoresis was performed on a 2% NuSieve® agarose : agarose (1:3) gel, and the DNA was visualized by ethidium bromide staining and ultraviolettransillumination.