

## Intravenous Ibuprofen (IV-ibuprofen) Controls Fever Effectively in Adults with Acute Uncomplicated *Plasmodium falciparum* Malaria but Prolongs Parasitemia

Srivicha Krudsood, Noppadon Tangpukdee, Polrat Wilairatana, Nantaporn Pothipak, Chatnapa Duangdee, David A. Warrell,\* and Sornchai Looareesuwan†

Department of Tropical Hygiene, Department of Clinical Tropical Medicine, Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Nuffield Department of Clinical Medicine, University of Oxford, United Kingdom

**Abstract.** Because some febrile patients are unable to swallow or retain oral antipyretic drugs, we carried out a double-blind, placebo-controlled trial in which intravenous ibuprofen (IV-ibuprofen) was given to adults hospitalized with fever associated with acute uncomplicated falciparum malaria treated with oral artesunate plus mefloquine. Thirty patients received IV-ibuprofen 400 mg and 30 received placebo every 6 hours for 72 hours. Reduction in the area above 37.0°C versus time curve was significantly greater for IV-ibuprofen than for placebo during the first 72 hours after first administration. No patients developed severe malaria; parasite clearance was delayed in the patients whose fevers were controlled by IV-ibuprofen (median 37.3 hours versus 23.7 hours in the placebo group [ $P = 0.0024$ ]). This difference did not appear to be clinically important. Adverse events, none considered severe, occurred equally in both groups. IV-ibuprofen was effective and well tolerated in reducing fever in febrile inpatients with malaria.

### INTRODUCTION

Fever is one of the commonest and most distressing symptoms of malaria, associated with chills (rigors), sweating, malaise, weakness, and anorexia. Patients with cerebral malaria may deteriorate when their fever rises.<sup>1</sup> Body temperatures exceeding 38.5°C are associated with an increased incidence of convulsions especially in children, delirium with temperatures between 39.5 and 40.0°C, and coma with temperatures above 42.0°C.<sup>2,3</sup> Hyperthermia may cause permanent severe neurological damage and is also associated with evidence of fetal distress in pregnant women with malaria.<sup>4</sup> Fever is often sufficiently unpleasant to demand palliation using physical methods of cooling and/or antipyretic drugs.<sup>5</sup> Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and paracetamol (acetaminophen) are all available as tablets, and there are some rectal and topical formulations.

However, some hospitalized patients require parenteral antipyretic therapy because they cannot swallow tablets or retain rectal suppositories and there are limited options available to treat these patients. Intravenous aspirin had no measurable effect on fever or parasite clearance in patients treated for malaria in Germany.<sup>6</sup> In many developing countries, metamizole (“Dipyrone”) injection is still used routinely despite concerns over the risk of agranulocytosis.<sup>7</sup> Recently, an IV formulation of the NSAID ibuprofen has been under investigation for the relief of fever in adults. It is thought to reduce fever by inhibiting prostaglandin (principally PGE<sub>2</sub>) synthesis by cyclooxygenases (e.g., COX-2 under inflammatory conditions) in the arachidonate cascade.<sup>8–12</sup>

In clinical trials, IV-ibuprofen reduced fever, pulse rate, and lactic acidosis in patients with sepsis and was not associated with significant nephrotoxicity, gastrointestinal (GI) bleeding, transfusion requirements, or other serious adverse events (SAEs).<sup>9,12</sup>

This study was undertaken to evaluate the efficacy and tolerability of IV-ibuprofen in the treatment of fever associated

with uncomplicated *Plasmodium falciparum* malaria treated with artemisinin combination therapy (ACT) in hospitalized adult patients.

### PATIENTS AND METHODS

The prospective double-blind, placebo-controlled study was carried out at the Bangkok Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand between April 29 and July 16, 2002, antedating the requirement for registration of clinical trials (Food and Drug Administration Amendments Act of 2007).

**Patients.** Patients were recruited from those attending the outpatient department of the hospital complaining of undiagnosed fever. Malaria diagnosis was carried out in the department with a delay of approximately 1 hour for getting the results. Those with microscopy-proven acute *P. falciparum* malaria were immediately admitted to the hospital and started on optimal antimalarial treatment (see later). Patients invited to join the study were more than 17 years of age, of either sex, who had an oral temperature > 38.0°C (100.4°F), and had been febrile for at least 12 hours, making antipyretic medication appropriate. The two highest temperatures at least 1 hour apart in the 12 hours before dosing were recorded. Those who refused were given identical antimalarial treatment and oral antipyretic treatment as required.

Excluded from the study were patients weighing < 40 kg; those who had received antipyretic drugs 8 hours or less before dosing; had any history of adverse reactions to any NSAID; were pregnant or nursing; had any features of severe malaria and had any other significant additional medical problems.<sup>13</sup>

Informed consent for the study was obtained from the patients or their guardians before enrollment into the study. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

**Interventions and assessments.** Sixty patients were enrolled and randomized sequentially using a table of random numbers in a 1:1 ratio to receive either IV-ibuprofen 400 mg or placebo infused every 6 hours for 72 hours, followed by doses every 6 hours as needed for a further 2 days to treat fever > 38.0°C (100.4°F).

\* Address correspondence to David A. Warrell, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK. E-mail: david.warrell@ndm.ox.ac.uk

† Deceased.

Clinical evaluation including neurological examination was carried out daily. Temperature, vital signs, laboratory measurements, parasitemia, adverse events (AEs), and concomitant medications were monitored and recorded during the 5-day treatment period. During the post-treatment period, safety monitoring was continued on Days 7, 14, and 21. Malarial blood films were examined every 4 hours until negative and daily thereafter until Day 28. The parasite clearance time (PCT) was measured as the interval from the start of antimalarial treatment until the asexual malaria parasite count fell below detectable levels in a peripheral blood smear. Fever clearance time (FCT) was taken as the period from the start of treatment with IV-ibuprofen or placebo until the oral temperature decreased to 37.5°C and remained below this temperature for the next 48 hours. Cure rate at Day 28 was defined as the absence of parasite recrudescence during 28 days of follow-up.

**Drug treatment.** Immediately on admission to the ward, patients were treated for acute uncomplicated falciparum malaria with both oral artesunate (4 mg/kg/day) and mefloquine (8 mg/kg/day for 72 hours).<sup>14</sup> They were randomized to receive either: 1) ibuprofen by intravenous infusion over 30 minutes (400 mg ibuprofen (4 mL) diluted in 100 mL of isotonic saline or 2) placebo intravenous infusion of 100 mL isotonic saline. IV-ibuprofen was supplied as a clear, colorless liquid in 5-mL glass vials, each containing 400 mg ibuprofen in a total volume of 4 mL (Cumberland Pharmaceuticals, Nashville, TN).

A case was defined as a "pyrexia treatment failure" if the temperature exceeded 41.1°C (106.0°F) during the treatment period after  $\geq 2$  hours following the first dose of IV-ibuprofen or placebo or if during the treatment period, the temperature exceeded 39.4°C (103.0°F)  $\geq 2$  hours after the second or subsequent doses of treatment. At the discretion of the investigator, a patient deemed to be a treatment failure could receive rescue treatment with fanning, air conditioning, and/or tepid sponging.

Blood for baseline safety laboratory assessments (biochemistry, hematology, blood coagulation) was collected from all patients before dosing and then on Days 1–5, 7, 14, and 21. Laboratory assessments were performed by the Hospital for Tropical Diseases.

**Efficacy endpoints.** The primary outcome measure was clinical response of fever to multiple doses of 400 mg IV-ibuprofen (versus placebo), assessed as the area above the 37.0°C (98.6°F) temperature versus time curve (AUC-T°) within the first 24 hours of treatment.

Secondary endpoints were effects of IV-ibuprofen and placebo on *P. falciparum* clearance time, defined as the interval between the start of treatment and the first negative blood smear; effects of multiple doses of 400 mg IV-ibuprofen (versus placebo) on the AUC-T° above a target temperature of 37.0°C (98.6°F) within the first 4 hours (0–4) and the first 24–72 hours (0–24; 0–72) of treatment; and the effects of IV-ibuprofen (versus placebo) on the number (%) of pyrexia treatment failures as defined above.

**Tolerability and safety endpoints.** The tolerability of IV-ibuprofen (and placebo) was determined as the number (%) of treatment-emergent AEs appearing for the first time or worsening on treatment, and the number (%) of AEs prompting premature study discontinuation. Safety was assessed by the number (%) of patients with SAEs, and by changes from baseline in temperature, other vital signs, and laboratory measurements.

**Sample size and blinding.** Sixty patients were randomized to the two treatment groups. Based on estimates of variance of AUC-T°, a total of 60 patients would be adequate to discern, at  $\alpha = 0.05$  and a power of 90% ( $\beta = 0.90$ ) a 12°C difference per hour in AUC-T° over the first 24 hours of treatment. A scheduled interim analysis to determine the need for additional patients was not conducted, because none of the enrolled patients had a fever  $> 38.0^\circ\text{C}$  (100.4°F) after the 72-hour dose of IV-ibuprofen or placebo. Patients, investigators, nursing staff, and study monitoring staff including microscopists were all blinded to study treatments.

**Statistical methods.** Continuous data were presented as mean, SD, or standard error of the mean (SEM). Categorical data were presented as numbers (%) of patients in each treatment group. The linear trapezoidal rule was used to calculate the primary and secondary AUC-T° efficacy objectives using all available data for each patient. Analysis of covariance was used to compare differences in AUC-T° between the two treatment groups. The treatment-by-baseline value interaction was investigated with baseline temperature being the mean of the qualifying temperatures and the temperature immediately before dosing. Primary efficacy endpoints were analyzed for patients in the efficacy-evaluable population only. Pyrexia treatment failures at endpoint were analyzed using the Cochran-Mantel-Haenszel procedure. Because parasite clearance times were not normally distributed, Wilcoxon two-sample and Kruskal-Wallis tests were used to compare the two treatment groups. Secondary efficacy endpoints were analyzed for all patients who were included in the safety population and had a baseline and  $\geq 1$  post-baseline assessment of the primary endpoint, no major protocol violations related to eligibility criteria or study conduct and all primary efficacy assessments.

Adverse events were summarized, by body system and preferred terms within body system, using the Medical Dictionary for Regulatory Activities (MedDRA). Each AE was counted only once for each patient and graded as mild, moderate, or severe by standard conventions. Serious AEs were defined as fatal, life-threatening, or resulting in prolonged hospitalization or persistent or significant disability/incapacity.

All statistical tests were conducted using SAS version 9.0 or higher (SAS Institute, Cary, NC). All statistical tests were two-tailed and *a priori* with  $\alpha = 0.05$ .

## RESULTS

**Patients.** All of the 60 patients were originally from malarious border areas of Thailand who had recently moved to work in factories in Bangkok and nearby cities such as Samutsonkram. After becoming feverish they had sought diagnosis and treatment at The Hospital for Tropical Diseases because of its reputation for being the best hospital in Thailand for managing malaria.

**Patient disposition.** Of the 60 patients randomized, 30 received IV-ibuprofen and 30 placebo. Forty-eight were male and 12 female, 18 to 54 years of age. All 60 patients enrolled in this study received a total of 12 doses each over the 72-hour treatment period, although one patient failed to complete the study for purely social reasons. No patient was withdrawn because of an AE and no patient required administration of IV-ibuprofen (or placebo) after 72 hours.

**Baseline characteristics.** Patients in the two treatment groups were similar in their demographic and clinical features

TABLE 1  
Baseline characteristics\*

	IV-ibuprofen group	Placebo group
	(N = 30)	(N = 30)
Males/females, n/n	24/6	24/6
Age range, years (mean ± SD)	18–54 (32.4 ± 9.24)	18–52 (27.8 ± 9.42)
Weight, kg (mean ± SD)	45.0–67.0 (55.4 ± 5.52)	43.0–83.0 (53.2 ± 8.57)
Temperature range, °C (mean ± SD)	38.2–39.5 (38.7 ± 0.34)	38.2–40.0 (38.8 ± 0.51)
Pulse rate, beats/min (mean ± SD)	72–108 (88.7 ± 8.1)	78–120 (93.9 ± 11.7)
Respiratory rate, breaths/min (mean ± SD)	20–24 (21.3 ± 1.4)	20–24 (21.7 ± 1.8)
Mean arterial pressure, mm Hg (mean ± SD)	70–100 (79.7 ± 7.2)	63–93 (82.2 ± 8.2)

\*Data for all randomized patients were analyzed.

(Table 1), exhibiting symptoms and signs typical of malaria, such as headache, dizziness, asthenia, fatigue, fever, nausea, anorexia, vomiting, diarrhea, abdominal pain, and myalgia. Their baseline temperatures averaged 39°C (102°F).

**Efficacy.** *Antimalarial treatment.* No patient had received antimalarial treatment before recruitment. All patients became a parasitemic within 3 days of starting treatment with artesunate and mefloquine as in previous studies.<sup>15,16</sup> No RI, RII, or RIII malaria treatment failures were encountered.<sup>17</sup> Parasite clearance was delayed in the patients whose fevers were controlled by IV-ibuprofen (range 14.0–50.0 hours, median = 37.3 hours compared with range 13.5–50.0 hours, median 23.7 hours in the placebo group ( $P = 0.0024$  Kruskal-Wallis test)).

*Fever control.* Treatment with IV-ibuprofen was associated with a significant reduction in the primary endpoint (AUC-T° [0–24 hours]) compared with placebo ( $P = 0.002$ ; Table 2). The times for the mean temperature to fall below 37.0°C were 3 hours for IV-ibuprofen and 20 hours for placebo (Figure 1). Treatment-related reductions in other, secondary efficacy endpoints with IV-ibuprofen (versus placebo) were also statistically significant at  $P < 0.0001$  for AUC-T°C (0–4 hours) and  $P = 0.0176$  for AUC-T° (0–72) (Table 3). Two pyrexia treatment failures occurred in the IV-ibuprofen group (6.7% of patients) and 3 (10.0%) in the placebo group, a difference that was not significant.

**Tolerability.** Treatment was well tolerated. Similar numbers of patients reported AEs in both treatment groups and no significant differences were found for the incidence of any AE subtype between treatment groups. A total of 31 AEs were reported in 26 patients with 16 of these AEs reported by

14 patients who received IV-ibuprofen and the remaining 15 reported by 12 patients who received placebo. GI disorders, particularly abdominal pain, were the most frequent AE, followed by respiratory disorders, particularly nasal congestion. There was no difference between treatment groups in the number or severity of gastrointestinal adverse events, as 6/30 (20%) IV-ibuprofen-treated patients and 6/30 (20%) placebo-treated patients experienced gastrointestinal adverse events all of mild to moderate severity. Additionally, none of the patients developed GI hemorrhage during the study. All AEs were mild or moderate and were judged by researchers to be attributable to the underlying disease, malaria, and unrelated to treatment.

**Safety.** There were no deaths, SAEs, or events resulting in premature study withdrawal. Individual serum biochemistry and other laboratory values in both treatment groups that fell outside reference ranges were attributable to the underlying disease, falciparum malaria. There were no statistically significant differences between the two treatment groups in frequencies of changes in clinical laboratory measurements from baseline to the end of the study, and no abnormal laboratory value was deemed to be of clinical significance. Vital signs remained within limits accepted by the researchers during the treatment and post-treatment intervals, and there were no clinically significant trends in these measures.

## DISCUSSION

In this study, IV-ibuprofen proved an effective and well-tolerated antipyretic agent in adults hospitalized with uncomplicated falciparum malaria. Frequencies of AEs, none severe, were similar in the groups given IV-ibuprofen and placebo. No patient discontinued treatment prematurely because of an AE, or exhibited any clinically significant changes in vital signs or laboratory data, apart from the marked reductions in body temperature with IV-ibuprofen.

These findings extend other previously reported data. The antipyretic efficacy of ibuprofen suspension during the early phase of uncomplicated falciparum malaria management has been shown previously.<sup>18,19</sup> Ibuprofen proved significantly more effective than paracetamol in lowering body temperature during the first 4.5 hours after dosing.<sup>18</sup> Another study assessed ibuprofen in 50 Gabonese children with uncomplicated falciparum malaria and found that the antipyretic efficacy of ibuprofen syrup compared with placebo was not significantly different across two fever thresholds.<sup>19</sup> However, the overall duration of fever and AUC-T° were significantly lower in patients receiving the ibuprofen (7 mg/kg q8 hr) compared with placebo.<sup>19</sup>

TABLE 2

Effects of treatments on AUC-T°\* (0–24 hours) (primary efficacy endpoint)

Variable	Treatment group	
	IV-ibuprofen (N = 30)	Placebo (N = 30)
AUC-T° (0–24 hours) (°C × hour), mean ± SD	7.49 ± 7.94*	16.44 ± 11.60
Baseline temperature °C, mean ± SD	38.69 ± 0.34	38.81 ± 0.51
Number (%) of subjects with AUC-T° (0–24 hours) in range:		
< 8°C × hour	20 (67%)	10 (33%)
(8–16) °C × hour	4 (13%)	4 (13%)
(16–24) °C × hour	4 (13%)	8 (27%)
> 24°C × hour	2 (7%)	8 (27%)

\*AUC-T° = area above the temperature 37.0°C (98.6°F) vs. time curve.

From an analysis of covariance with effects caused by treatment and baseline temperature, the difference in AUC-T° (0–24) between treatments is 8.14°C × hour, a significant reduction for IV-ibuprofen compared with placebo ( $P = 0.0019$ ).

TABLE 3  
Effects of treatments on AUC-T° over other intervals (secondary efficacy endpoints)

Variable	Interval, hour		
	0 to 4	0 to 72	24 to 72
IV-ibuprofen group: AUC-T°, mean ± SD	2.40 ± 1.54	8.85 ± 11.03	1.36 ± 4.00
Placebo group: AUC-T°, mean ± SD	5.18 ± 2.97	16.94 ± 12.23	0.50 ± 1.51
AUC-T° effect caused by treatment (IV-ibuprofen–placebo)	-2.49 ( $P < 0.0001$ )	-7.18 ( $P = 0.0176$ )	0.96 ( $P = 0.2284$ )
AUC-T° change per °C baseline T°	2.32 ( $P = 0.0008$ )	7.60 ( $P = 0.0303$ )	0.86 ( $P = 0.3558$ )

AUC-T° = area above the temperature 37.0°C (98.6°F) vs. time curve; T° = temperature.

In our study, IV-ibuprofen compared with placebo lowered body temperature, especially within the 4 hours after the first dose. There was no appreciable AUC-T° difference between IV-ibuprofen and placebo between 24 and 72 hours, consistent with the fact that all patients in our study had uncomplicated *P. falciparum* malaria that was cured with a highly effective artemisinin combination therapy.

An interesting finding in this study was the significant delay in parasite clearance in the IV-ibuprofen-treated patients, which had no clinically detectable deleterious effect. In Gabonese children with *P. falciparum* malaria, paracetamol also delayed parasite clearance without proving any better than purely mechanical methods of fever control.<sup>20</sup> The authors suggested that the mechanism by which paracetamol prolonged parasitemia was by decreased inducible tumor necrosis factor (TNF), interleukin (IL)-6 production and oxygen radicals.<sup>20</sup> However, other studies in Tanzanian children with uncomplicated *P. falciparum* malaria, were unable to find any relationship between the anti-pyretic effects of paracetamol or chloroquine and changes in cytokines or inflammatory/anti-inflammatory cytokine levels or Th1/Th2 ratios.<sup>21</sup> Another study found that an anti-TNF monoclonal antibody produced a dose-dependent reduction in fever in Gambian children with *P. falciparum* malaria without affecting parasite clearance.<sup>22</sup> In a large randomized controlled trial (RCT), a different anti-TNF monoclonal antibody failed to reduce mortality in Gambian children with severe malaria but significantly increased the incidence of neurological sequelae.<sup>23</sup> Finally, a pilot study of a polyclonal Fab fragment of an anti-TNF antibody in Thai adults did not suggest any useful effect in adults with cerebral malaria.<sup>24</sup>

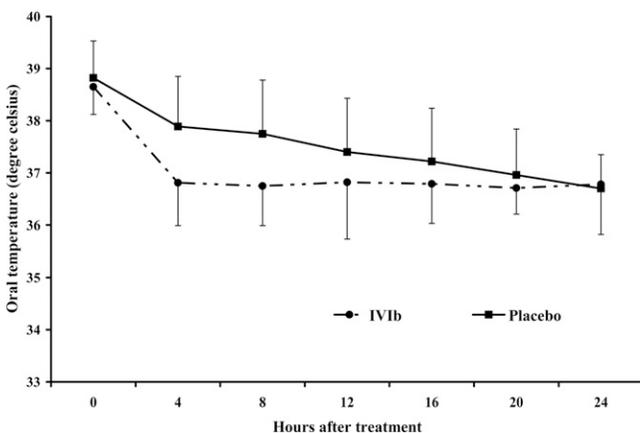


FIGURE 1. Mean oral temperature profiles in patients with malaria given IV-ibuprofen. IV-ibuprofen  $N = 29$  and placebo  $N = 30$ ; vertical bars represent one standard deviation of mean.

Three possible explanations for our finding of fever reduction and lengthened parasitemia in ibuprofen-treated patients would be 1) a direct effect of fever on parasite growth, 2) depression of inflammatory cytokine production by ibuprofen delaying parasite clearance, and 3) reduced cytoadherence of parasitized red blood cells.<sup>25-33</sup> One study found that increasing temperature suppressed the growth of *P. falciparum* parasites in *in vitro* culture and the authors further postulated that host temperature and cytokines combine with immunological mechanisms to control parasite growth.<sup>25</sup> Malarial fever is also thought to be caused partly by TNF and other pyrogenic cytokines released as part of the host immune system's response to products of schizont rupture.<sup>25-28</sup> In addition to class effects of NSAIDs on COX enzymes, ibuprofen may also influence output of TNF- $\alpha$ .<sup>29-32</sup> In murine models, ibuprofen not only attenuates TNF- $\alpha$  secretion but also reduces glutathione depletion and hepatic apoptosis and increases longevity.<sup>32</sup> Another possible mechanism by which reduction of fever might delay parasite clearance is reduced cytoadherence of parasitized red blood cells. Febrile temperatures were found to induce cytoadherence of ring-stage *P. falciparum*.<sup>33</sup>

## CONCLUSION

This study of IV-ibuprofen is the first to document a decisive effect of an anti-pyretic drug against malarial fever. IV-ibuprofen at a dose of 400 mg has significant and rapid antipyretic effects and was well tolerated in hospitalized patients with malarial fever. IV-ibuprofen also increased parasite clearance time. Future studies are warranted in larger and more diverse patient populations.

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Authors' addresses: Srivicha Krudsood, Department of Tropical Hygiene, Mahidol University, Bangkok, Thailand. Noppadon Tangpukdee and Polrat Wilairatana, Department of Clinical Tropical Medicine, Mahidol University, Bangkok, Thailand. Nantaporn Pothipak and Chatnapa Duangdee, Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. David A. Warrell, Nuffield Department of Clinical Medicine, University of Oxford, UK.

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