Effect of Antipyretic Drugs in Children with Malaria

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A comparison of different antipyretics in children with malaria showed a small effect of naproxen, but not of metamizol, on the reduction of fever peaks. Antipyretic treatment had no effect on fever clearance and therefore should be used cautiously in the treatment of malaria.

Fever is the most apparent sign during an acute malaria attack and can be accompanied by other nonspecific symptoms such as headache, diarrhea, abdominal pain, vomiting, and nausea. The physiological role of fever in malaria and other infectious diseases remains unclear [1], and the value of reducing fever in children with malaria is controversial [2]. To control fever, the World Health Organization [3] recommends mechanical measures such as fanning, tepid sponging, and cooling blankets. In addition to antimalarial chemotherapy, patients usually also receive antipyretic treatment to keep fever low [4], despite growing doubts about the need for this practice [5].

Data from Kwiatkowski [6] and our own recent in vitro data show that increased temperatures, which correspond to febrile temperatures in humans, inhibit the growth of Plasmodium falciparum. It seems that malarial fever is a beneficial reaction of the host to combat the infection by killing or inhibiting growth of the parasite. Thus, reducing fever could have negative effects on the course of the disease.

We first attempted to test this hypothesis in children treated with acetaminophen [7]. However, it was not possible to reduce malarial fever with this drug, and treatment with acetaminophen was even associated with prolonged parasite clearance times, possibly by decreasing the production of TNF and oxygen radicals.

The present study investigated the relationship among fever, parasite clearance, and immunologic markers (production of cytokines and oxygen radicals) with use of 2 other nonsteroidal antipyretic drugs. Metamizol, a pyrazolone derivative, was chosen because it is widely used to treat fever in Africa. Naproxen, a propionic acid derivative similar to ibuprofen, was used because of its reported efficacy against childhood fevers [8]. Both agents have a similar mode of action through the inhibition of cyclo-oxygenase and subsequent prostaglandin synthesis.

Methods. The study was done at Albert Schweitzer Hospital in Lambarené, Gabon, which is located in an area where P. falciparum is highly endemic [9]. Patients attending the outpatient clinic between October 1997 and July 1998 were included in the study if they had uncomplicated P. falciparum malaria and met the following criteria: 2–7 years of age; asexual parasitemia (20,000–200,000 parasites/µL of blood); temperature of >38°C at admission or fever during the preceding 24 h; no antipyretic treatment during the preceding 8 h; and no effective antimalarial treatment for the current infection, as confirmed by urine tests for chloroquine and quinine (Wilson and Edeson test) and for sulfonamides (Lignin test). Because of the high level of chloroquine resistance in the area, patients with a history of treatment with low doses of chloroquine were eligible for inclusion in the study. Patients were not included in the study if they had complicated malaria, as defined by any of the following criteria: hemoglobin level, <8.0 g/dL; packed-cell volume, <24%; leukocyte count, >12 × 10⁷ cells/L; glucose level, <50 mg/dL; lactate level, >3.5 mM; schizontemia, >50 shizonts/µL; platelet count, <50 × 10⁹ cells/L; and signs of other concomitant infection or other severe disease. Patients with >2% pigment-containing neutrophils were excluded from the study, to prevent the enrollment of patients with highly synchronized parasite populations hidden in the deep vasculature [10, 11]. Children were excluded from the study when they had a history of febrile or afebrile convulsions.

Patients were hospitalized until 2 successive thick blood smears were negative. All patients received an infusion of 5% glucose with 12 mg/kg of quinine dihydrochloride every 12 h.
A single oral dose of sulfadoxine/pyrimethamine was given at the time of discharge.

Patients were randomly assigned to 1 of 3 antipyretic treatment groups by means of a random-numbers table: mechanical antipyretic treatment consisting of continuous electric fanning and tepid sponging when rectal temperatures rose above 37.5°C; metamizol treatment administered by mouth at a dosage of 10 mg/kg every 6 h, in addition to mechanical antipyresis as described above; and naproxen treatment administered as rectal suppositories at a dosage of 7.5 mg/kg every 12 h, in addition to mechanical antipyresis as described above. Expelled suppositories were immediately readministered.

At the time of admission (day 0) and each subsequent day, complete physical examination was done, and signs and symptoms were recorded. Rectal body temperature was measured at admission and then hourly until discharge (in 19 cases, temperature was measured only every 6 h). Parasitemia was measured through a Giemsa-stained thick blood smear by a direct method described elsewhere [12]. This was performed on admission and then every 6 h until 2 consecutive blood smears were negative. Capillary blood samples were obtained on days 0 and 3 for laboratory examination, to determine the following: hemoglobin level, packed-cell volume, leukocyte and platelet counts, glucose level, and lactate level.

Venous blood samples (3 mL) were obtained in EDTA-containing tubes before the start of treatment and 24, 48, and 72 h thereafter for the measurement of plasma levels of TNF, IFN-\(\gamma\), IL-10, and IL-12. In addition, TNF levels were measured, at the same times, in supernatants of stimulated whole blood. Immediately after venipuncture, 2 mL of whole blood was stimulated with phytohemagglutinin (10 \(\mu\)g/mL; Sigma) or lipopolysaccharide (0.1 \(\mu\)g/mL; Sigma). After 2 h of incubation at 37.5°C, supernatants were harvested and stored at −20°C until measurement of cytokine levels. All cytokine levels were determined by ELISA (Flexia, Biosource) according to the manufacturer’s instructions.

Immediately after venipuncture, the production of oxygen radicals was measured by addition of 10 \(\mu\)L of whole blood to Krebs-Ringer-phosphate-glucose buffer containing 0.1 \(\mu\)g/mL phorbolmyristate acetate (Sigma) and 11 \(\mu\)M luminol (Sigma) [13]. Luminescence was measured with a luminometer (Lumat, EG&G Berthold). The induction of oxygen radicals was expressed in relative light units per second and was recorded every 5 min until peak values were reached.

Parasite clearance time was defined as the time in hours from admission until the first of 2 consecutive negative thick blood smears. Fever was assessed in 2 ways: fever clearance time, defined as duration in hours from admission to the first time a patient’s temperature stabilized below an indicated fever threshold; and fever time, defined as duration in hours that an individual’s temperature was above an indicated fever threshold. A patient with only 1 fever peak very late in the course of infection would thus have a long fever clearance time but a short fever time. This form of analysis was done because our in vitro study had shown that the extent of inhibition of growth of \(P. falciparum\) depends on the time of exposure to febrile temperatures (authors’ unpublished data).

Differences between the treatment groups were assessed by the Kruskal-Wallis nonparametric test or by analysis of variance with Dunnett’s procedure for post hoc comparisons. The Wilcoxon signed rank test was used to assess differences between time points within a group. Correlations were calculated using Spearman’s rank correlation. Two-sided \(P\) values of <.05 were considered significant.

Results. Ninety patients (30 patients per group) were enrolled in the study. The 3 groups were similar at admission with respect to demographics and clinical and laboratory data (data not shown). All children recovered completely, and there were no differences in terms of adverse events during hospitalization in the 3 treatment groups.

At the time of admission, rectal temperatures were similar in all 3 groups. After the start of treatment, 28, 29, and 27 patients in the mechanical antipyretic, metamizol, and naproxen treatment groups, respectively, had temperatures of >38.0°C, and 14, 10, and 14 patients, respectively, had temperatures of >40°C. In contrast to metamizol, naproxen consistently reduced fever clearance times over a wide range of fever thresholds (37.8°C, 38°C, 38.5°C, and 39.5°C). However, this reduction was significant only at a fever threshold of 38.0°C (mechanical antipyresis, 39 h; metamizol treatment, 39 h; naproxen treatment, 24 h; figure 1). The fever time was significantly lower for children receiving naproxen treatment (4.5 h at a fever threshold of 38.5°C; \(P = .009\)) than for those receiving mechanical antipyresis (10.4 h at a fever threshold of 38.5°C).
This finding was significant over a wide range of fever thresholds (37.8°C, 38°C, 38.5°C, 39°C, 39.5°C, and 40°C). Treatment with metamizol led to shortening of the fever time at any fever threshold (6.8 h at a fever threshold of 38.5°C), but this decrease was never significant compared with that associated with mechanical antipyresis.

At admission, body temperature and parasitemia were significantly correlated \( (r = .34; P = .002) \). Twelve and 18 h after the onset of therapy, however, they were clearly inversely correlated \( (r = -.46, P < .001 \) and \( r = -.26, P = .015 \), respectively).

The mean time to parasite clearance was 63 h, with no significant difference in the time to parasite clearance in any treatment group (mechanical antipyresis, 60 h; metamizol treatment, 63 h; naproxen treatment, 66 h). Even though parasitemia in the mechanical treatment group was consistently lower than that in the naproxen treatment group during the first 30 h of treatment, the difference was not significant (figure 2). The initial clearance of parasitemia was faster in the mechanical treatment group, in which parasitemia already had decreased significantly 6 h \( (P = .047) \) and 12 h \( (P = .008) \) after the start of treatment, compared with parasitemia at admission. In both the metamizol and naproxen treatment groups, a significant decrease was first observed 18 h after the start of treatment.

A simple correlation between fever and parasite clearance times is not meaningful, since long courses of parasitemia necessarily lead to long courses of fever, as shown by a positive correlation between the 2 variables in our study \( (r = .74; \text{fever threshold, } 38.5^\circ C) \). To determine the effect of fever on the course of parasitemia, we corrected for the duration of parasitemia by calculating the proportion of time with parasitemia during which fever occurred (fever time/parasite clearance time). No correlation between the corrected fever time and the parasite clearance time was found for any fever threshold \( (r = .02; \text{fever threshold, } 38.5^\circ C) \).

In all patients, plasma levels of the cytokines TNF, IFN-\( \gamma \), IL-10, and IL-12 were elevated at admission. No significant differences among the treatment groups were seen at any time point.

Parasitemia at admission was significantly positively correlated with plasma levels of TNF \( (r = .28) \) and IL-10 \( (r = .43) \) and negatively correlated with plasma levels of IL-12 \( (r = -.25) \). On all 3 days, temperature was highly correlated with plasma levels of both IL-10 \( (r = .78 \text{ on day 1 to } r = .44 \text{ on day 4}) \) and IFN-\( \gamma \) \( (r = .29 \text{ on day 1 to } r = .39 \text{ on day 4}) \). No consistent correlations over time were found with the other cytokines.

There were no significant differences in phagocytosed TNF- and lipopolysaccharide-induced TNF concentrations between the 3 treatment groups at any time. A common feature in all 90 cases was that ex vivo cytokine production 48 h after the onset of therapy was significantly greater than cytokine production at admission.

Lipopolysaccharide-induced TNF production at admission was significantly inversely correlated with parasite clearance time \( (r = -.30; P = .028) \).

There were no significant differences in production of oxygen radicals between the 3 antipyretic treatment groups on any day. Peak production and the time of peak production were also similar in the 3 treatment groups (data not shown).

**Discussion.** A previous study from our group showed that it is not possible to reduce malarial fever with acetaminophen [7]. In the present study, drugs with antipyretic properties that are generally thought to be superior to those of acetaminophen were used to determine whether it is possible to reduce malarial fever and whether a reduction has an effect on the course of parasitemia. The results show that treatment with naproxen can, to some extent, lead to faster fever clearance than treatment with metamizol, which had no effect. The antipyretic effect of naproxen was more pronounced, as shown by the drug’s ability to reduce a child’s fever time, suggesting that the drug exerts its effect mainly by suppressing fever peaks rather than by clearing malarial fever. If antipyretic treatment for malarial fever is desired, then naproxen is preferable to either acetaminophen or metamizol.

The question of whether reduction of fever is clinically meaningful remains. Animal studies have shown both the beneficial effect of fever and the negative effect of antipyretic treatment in the course of infectious diseases (reviewed in [14]).

Clinical studies involving humans suggested a beneficial effect of fever on sepsis [15] and bacterial peritonitis [16] and a negative effect of treatment with antipyretics on rhinovirus [17] and varicella-zoster virus [18] infections. The present study shows that differences in body temperature do not lead to differences in the course of *P. falciparum* parasitemia. This finding is surprising in view of the clear results of in vitro studies of this parasite, which showed a strong growth inhibitory effect.
at febrile temperatures [6]. The time spent with febrile temperatures may not have been long enough for a visible effect. Our in vitro studies showed that a 6-h exposure to temperatures of 40°C at late stages leads to significant growth inhibition. Longer exposure is needed to inhibit parasite growth at 39°C. In the present study, however, only 6 patients (7%) had a cumulative exposure to temperatures of >40°C for at least 6 h, and 20 (22%) had an exposure to temperatures of >39°C for this period of time. One reason for the small numbers of patients exposed to these temperatures might have been the exclusion of patients with severe malaria, who presumably would have higher temperatures or prolonged fever. Furthermore, an effect of fever on the course of parasitemia would be masked by the effect of quinine, which is undoubtedly much more effective against *P. falciparum* than are febrile temperatures; thus, a beneficial effect of fever on parasitemia perhaps could be seen in yet untreated malaria.

Antipyretics are commonly given to children with infectious diseases, to prevent febrile convulsions. However, with *P. falciparum* malaria, in which convulsions are common, more than one-half of convulsions occur at rectal temperatures of <38°C, suggesting that the infection, not the fever, induces convulsions (which thus cannot be prevented by reducing fever) [19].

Plasma levels of TNF and IFN-γ were, not surprisingly, associated with fever. In addition, we found a high correlation between plasma levels of IL-10 and body temperature. TNF leads to the production of IL-10, which suggests a rapid counterregulatory response to inflammatory and pyrogenic cytokines in these children with mild malaria [20].

Our earlier study showed decreased production of radical oxygen intermediates after acetaminophen treatment [7]. Treatment with naproxen or metamizol did not lead to a comparable phenomenon.

The positive correlation between temperature and parasitemia that we found at admission has been described earlier for a large population [21]. The initial drop in parasitemia was faster in the mechanical antipyretic treatment group than in the other treatment groups. The reason for this finding remains unexplained; however, the effect was not due to fever or production of cytokines or oxygen radicals, since there was no significant difference in these parameters between the treatment groups during the first 6 h of therapy. An effect of the drugs themselves was excluded by in vitro studies showing no effect of metamizol or naproxen treatment on the growth of *P. falciparum* (authors’ unpublished data).

Taken together, the benefits from not taking antipyretics do not seem large. However, the relative ineffectiveness of commonly used antipyretics, the high risk of overdosing [22], and the need to reduce drug interactions strongly argue against the widespread practice of giving adjuvant antipyretic drugs indiscriminately to every child with *P. falciparum* malaria.

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References