Pentoxifylline as a Supportive Agent in the Treatment of Cerebral Malaria in Children

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In an open, randomized, controlled therapeutic trial, 56 children with cerebral malaria (CM) were randomly assigned to receive standard quinine regimen with or without pentoxifylline (10 mg/kg/day by continuous intravenous infusion). Pentoxifylline exerted an inhibitory effect on the synthesis of tumor necrosis factor (TNF), a possible mediator of CM. The 26 children who received pentoxifylline had significantly shorter comas than controls (median, 6 vs. 46 h; $P < .001$). Pentoxifylline recipients showed a trend toward a lower mortality, with a borderline significant difference ($P = .055$). The better outcome in the pentoxifylline group was associated with a decline in TNF serum levels on the third day of treatment in a few subjects that was not seen in controls. While alternative or concurrent mechanisms of action may be of some relevance, larger double-blind trials are needed to determine whether pentoxifylline has a therapeutic role in CM.

Most mortality associated with *Plasmodium falciparum* infection is caused by cerebral malaria (CM) [1]. Even with the best chemotherapeutic regimens and the most appropriate management of associated disorders, CM has a mortality rate of 5%–38% [2, 3] in children, with occasional neurologic sequelae in survivors [4].

The pathophysiology of CM is not completely understood; obstruction of brain vessels by parasitized erythrocytes, which display a unique capacity to bind to endothelial cells at the capillary level, is the most representative pathologic lesion [5]. However, a pathogenetic hypothesis based solely on microcirculatory failure does not explain why, unlike in cases of true ischemic neurovascular disorder, most CM survivors have no permanent neurologic damage [6].

Tumor necrosis factor (TNF) has been suggested as a possible pivotal mediator of CM [7]. While low levels of TNF seem to be associated with a beneficial effect on the host-parasite interaction, high levels of circulating TNF may cause the severe functional derangements seen in CM [8]. Malaria parasites can trigger TNF release from macrophages [9], and serum TNF levels correlate with disease severity and prognosis in both experimental [10] and human CM [11]. In several clinical studies on CM, the highest levels of TNF were found in patients who subsequently died; lower levels were proportionally associated with better outcomes [12, 13]. TNF induces hypoglycemia, lactic acidosis, and other metabolic disturbances [14] and it has been suggested that it may up-regulate parasite receptors on the endothelium of cerebral blood vessels and promoting adhesion of parasitized erythrocytes [15]. More recently, a pathophysiologic link was proposed in CM between TNF and the endothelial synthesis of nitric oxide [16]. High levels of TNF-induced nitric oxide could diffuse across the blood-brain barrier to nearby neurons, be misinterpreted as being of synaptic origin, and thus interfere with orderly neurotransmission. We can envisage how sequestered parasitized erythrocytes, as distinct from physically obstructing blood flow, could determine long-lasting coma from which patients may recover without stroke-like permanent dysfunctions.

Along with other molecules, pentoxifylline decreases TNF release from macrophages via the inhibition of phosphodiesterase and the increase of intracellular cyclic adenosine monophosphate [17]. In a murine malaria model (*Plasmodium berghei* ANKA–infected CBA/Ca mice), which shares some features with human CM, administration of pentoxifylline led to nondetectable concentrations of TNF and prevention of CM by the time 75% of the untreated controls began to develop CM. The latter also had high TNF serum levels [18]. In human volunteers, under controlled conditions of endotoxemia, pentoxifylline totally abolished the endotoxin-induced rise of TNF [19].

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Informed consent was obtained from patients' parents or guardians. Human experimentation guidelines of the ethics committees of the hospitals of Kiremba and the Institute of Immunology and Infectious Diseases, University of Verona, were followed in the conduct of the clinical research.

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Since pentoxifylline has been used widely in clinical settings [20] and there is significant experience with the safety of the drug in children [21], we undertook a randomized clinical trial to evaluate whether addition of pentoxifylline to standard quinine therapy could improve the outcome (i.e., the speed of recovery of full consciousness) of children with CM.

Patients and Methods

The study was done in the Hospital of Kiremba, Ngozi Province, in rural Burundi, in 1992 and 1993.

Study population. Patients were considered eligible for the study if they were <14 years old and met the diagnostic criteria for CM. The latter was defined as the presence of unrousable coma, asexual forms of *P. falciparum* in peripheral blood, and the absence of other causes of unconsciousness. Cerebral fluid samples had to lack evidence of bacterial infection. Patients with convulsions had to have a coma for ≥0.5 h that was monitored by investigators [22].

Demographic data and clinical histories were obtained from parents or guardians and included the patient's age and sex, history of convulsions before admission, and duration of preadmission coma. For practical reasons, the latter information was asked in terms of quarters of days (6 h), rather than hours, since few parents had watches or were accustomed to conventional time measurement.

At admission, we determined the degree of coma, glucose and hemoglobin (Hb) concentrations; level of parasitemia; body temperature, serum creatinine, nitrogen, and electrolyte levels; and white blood cell count.

Coma score was determined according to the Glasgow coma scale as described by Teasdale and Jennet [23]. Motor and verbal responses and eye movements were evaluated. The former were determined as the response to a painful stimulus: Those who localized the stimulus were scored as 2, those who withdrew the limb from pain as 1, and those who did not respond as 0. The verbal response (adapted for children not old enough to speak) was scored as 2 if a painful stimulus was followed by an appropriate vocal response or normal cry, 1 in cases of moans or inappropriate cry, and 0 if there was no response. Eye movements were evaluated by determining if the child could move the eyes to follow the mother's face or respond to a light stimulus; if able to do so, the score was 1; if there were unspecific or no eye movements, the score was 0. Patients considered eligible for the study had to have a total score ≤3.

Treatment. Intravenous catheters were inserted into all children studied. After rehydration with a 5% dextrose solution, all patients had a loading dose of quinine (20 mg/kg) infused over 4 h. All were then given quinine (10 mg/kg/8 h) for 7 days. After full recovery of consciousness, quinine was given orally at the same dosage. Blood transfusions were given in cases of severe anemia (Hb <5 g/dL).

The study was conducted in a nonblinded manner. Patients were randomly assigned (by random number tables) to receive standard quinine treatment with or without pentoxifylline: 10 mg/kg/day in physiologic saline solution through continuous intravenous infusion for the first 3 days of treatment. Those not in the pentoxifylline group received an additional infusion of physiologic saline or 5% dextrose solution, depending on the child's hydration balance and glycemia status. Pentoxifylline (5-mL vials) was administered as an injectable solution that contained 100 mg of drug (Hoechst Italia, Milan, Italy).

Assessment. Starting on the day of admission, the patient's consciousness was monitored in hours and assessed at least twice daily until full recovery (coma score 5). When a coma overtly resolved between two evaluations, this was recorded in the child's chart and confirmed at the subsequent evaluation. Thick blood films stained with Giemsa (1:10 dilution in buffered distilled water) were made daily as an approximate check of treatment effectiveness, and parasitemia was calculated on admission and every 2 days (until parasite clearance was confirmed on two subsequent evaluations).

TNF measurement. Serum samples for TNF assay were obtained at admission and on day 3 from 10 patients treated with pentoxifylline and from 7 controls. Sera were also obtained on day 4 from 4 pentoxifylline recipients and 3 controls. Blood was obtained with disposable pyrogen-free syringes and immediately transferred to 5-mL vials with 0.5 mL of sodium citrate. After centrifugation, sera were stored at −30°C before transfer to the Institute of General Pathology, University of Verona, where they were maintained at −81°C until TNF was assessed by immunoenzymatic assay [24]. This assay uses two mouse non–cross-reacting IgG1 monoclonal antibodies (B154.9 and B154.7; provided by G. Trinchieri, Wistar Institute, Philadelphia) directed against two distinct determinants of TNF-α. One (B154.7) was coupled to alkaline phosphatase according to standard protocols. An ELISA amplification system (Immunoselect; Life Technologies GIBCO BRL, Gaithersburg, MD) was used to enhance the TNF-α detection limit, which was 20 pg/mL in the final assay.

Statistical analysis. After enrollment, children were studied prospectively. On the basis of known rates of coma resolution with standard treatment, an expected improvement of 0.25, and a significance level of 5%, we anticipated we needed to study 100 patients to achieve an 80% power. The trial was designed to study 100 children, but enrollment was stopped in 1993 after 56 subjects were enrolled, because of ethnic disorders in Burundi. The Cox proportional hazards model was used to examine the relation between administration of pentoxifylline and time to recovery of full consciousness (measured in hours) and to compare outcomes of pentoxifylline recipients and controls. Since there were some tied times in the resolution of coma, an "exact" approach to the maximization of the likelihood function was used [25]. Treatments were also evaluated after stratification for degree of coma at time 0, duration of coma before enrollment, and hemoglobin concentration at time 0. Significance was always at the .05 level.

Results

Subjects. Fifty-six children were enrolled and given the standard quinine regimen. Twenty-six children also received pentoxifylline. Those who received quinine alone were considered controls. Table 1 shows baseline clinical and demo-

Table 1. Baseline characteristics of subjects at admission by treatment group.

	Quinine + pentoxifylline	*P*	Quinine
Age, mean	5.6		5.1
Median (SD)	4.8 (4.01)	NS	4 (3.93)
Males	15 (57.7)	NS	15 (50)
Females	11 (42.3)		15 (50)
Coma duration before admission (h), mean	14.07	NS	14.2
Median (SD)	12 (9.59)		12 (10.53)
Coma grade			
0	4 (15.4)		4 (13.3)
1	6 (23.1)	NS	7 (23.3)
2	10 (38.4)		12 (40)
3	6 (23.1)		7 (23.3)
Coma >24 h	7 (26.9)	NS	6 (20)
Convulsions	17 (65.4)	NS	22 (73.3)
Hemoglobin <5 g/dL	3 (11.5)	NS	3 (10)
Glucose <40 mg/dL	7 (26.9)	NS	8 (26.6)
Parasitemia >50,000/μL	14 (53.8)	NS	13 (43.3)
Age >3 years	10 (38.4)	NS	13 (43.3)
Subjects with associated diseases other than anemia*	6 (23.1)	NS	7 (23.3)

NOTE. Data are no. (%) unless otherwise indicated. NS, not significant.

graphic data; no significant differences were recorded between groups.

Coma resolution. Recovery of full consciousness was analyzed for all 56 patients. Median time to recovery was 6 h in the pentoxifylline group and 46 h in the control group ($P < .001$; figure 1, table 2). After adjustment for coma score at time 0, duration of coma before enrollment, and Hb concentration at time 0, the rate of recovery to full consciousness in the pentoxifylline group was 39 times higher than in the control group (95% confidence interval [CI], 11–138).

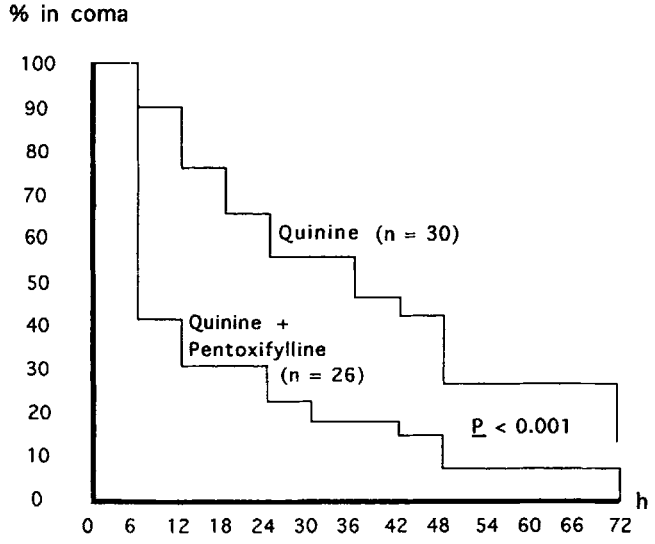

Figure 1. Duration of coma in children with cerebral malaria treated with quinine and pentoxifylline or quinine alone.

Table 2. Assessment of therapies (quinine plus pentoxifylline or quinine alone) for cerebral malaria in children by outcome.

	Quinine + pentoxifylline	*P*	Quinine
Median coma duration (h)	6	.001	46
Survival	26/26 (100)	.055	25/30 (83.3)
Neurologic sequelae	2/26 (7.7)	NS	2/25 (8)
Parasite clearance after 72 h	22/26 (84.6)	NS	24/25 (96)
Hours before 1st defervescence, mean	27.4		30.8
Median (SD)	24 (9.3)	NS	27 (13.4)

NOTE. Data are no. patients/no. treated (%) unless otherwise indicated and, except for survival and coma duration, refer to survivors only. NS, not significant.

Data on recovery of full consciousness were examined after patients were stratified according to degree of coma on admission (table 3). In the 13 patients with light coma (score 3), the estimated median time to regain full consciousness among the 6 given pentoxifylline was 3 h compared with 24 h for the 7 controls ($P < .001$). Among the 43 patients with deep coma (score, 0–2), the median time to full consciousness was significantly shorter ($P < .001$) in the pentoxifylline group (6 h) than in controls (48 h). As expected, the median times to regaining full consciousness were higher in subjects with deep than light comas in the pentoxifylline (6 vs. 3 h; $P = .032$) and control (48 vs. 24 h; $P = .003$) groups. The adjusted rate of recovery of full consciousness in the pentoxifylline group was 18.9 times that in the placebo group (95% CI, 2.1–170.0) in subjects with light coma versus 5.8 (95% CI, 2.6–13.3) in subjects with deep coma. The 5 patients who died were treated as "censored" at the time of their deaths.

Mortality. The study was not specifically designed to investigate a significant difference in mortality between the treatment groups. There were no deaths among the pentoxi-

Table 3. Recovery of full consciousness after stratification by degree of coma at admission in children treated with quinine plus pentoxifylline or quinine alone.

	Coma score 3		Coma score 0–2	
	Quinine + pentoxifylline	Quinine	Quinine + pentoxifylline	Quinine
No.	6	7	20	23
Median coma duration (h)	3	24	6	48
P	.001		.001	

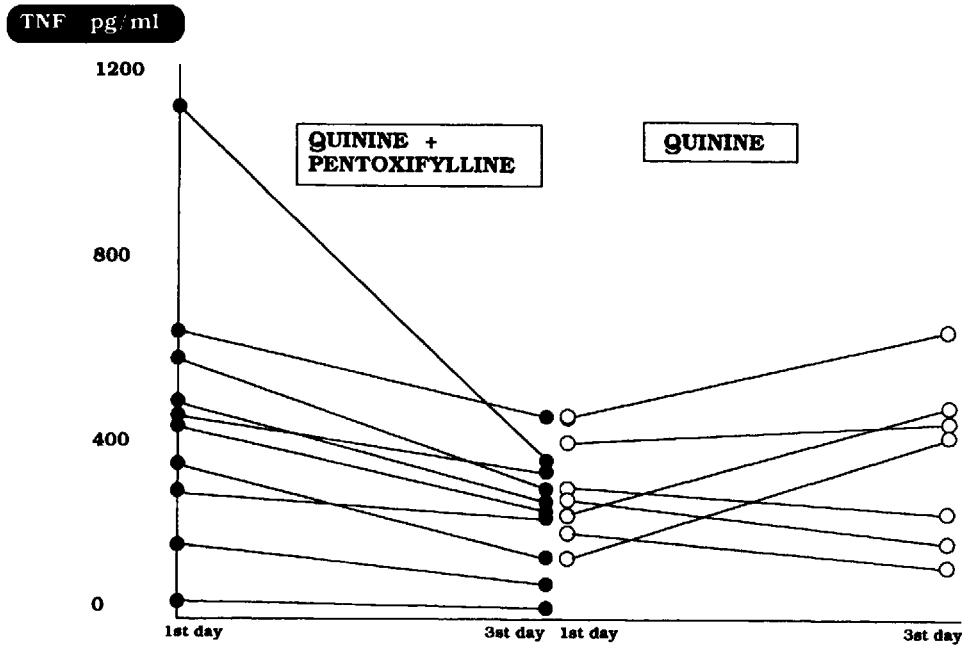

Figure 2. Variations in tumor necrosis factor (TNF) serum levels in children treated for cerebral malaria with quinine and pentoxifylline or quinine alone. Sera were obtained at admission and on day 3 of treatment.

fylline recipients and, although 5 (16.7%) of 30 children given quinine alone died, the difference was not significant ($P = .055$, Fisher's exact test, two-sided).

TNF serum levels. At admission, mean serum TNF levels were 432.5 pg/mL (range, 22–1103; SD, 283.2) in subjects who subsequently received pentoxifylline and 279.7 pg/mL (range, 130–434; SD, 169.3) in controls (SE, 106.7; not significant [NS]). While all pentoxifylline recipients tested had decreased TNF serum levels on day 3, 4 of 7 controls had increased values ($P < .01$; figure 2). TNF levels on day 3 showed a mean reduction of 203.1 pg/mL (SD, 206.9; $P < .02$) in subjects treated with pentoxifylline and a mean increase of 80 pg/mL (SD, 184.9; NS) in controls. The serum samples obtained on day 4 showed that 3 of 4 pentoxifylline recipients had small increases in TNF levels, and the 3 controls had decreased values.

Additional findings on outcome (survivors only). Twenty-two (84.6%) of 26 children treated with pentoxifylline cleared parasites from peripheral blood after 72 h as did 24 (96%) of 25 survivors in the control group (NS). The first defervescence occurred after a median of 24 h (mean, 27.4; SD, 9.3) in pentoxifylline recipients and of 27 h (mean, 30.8; SD, 13.4; NS) in controls. Two children in each group had neurologic sequelae (7.7% and 8.0% in pentoxifylline and control groups, respectively); neither had apparent permanent damage at 1 month of follow-up (table 2).

Side effects. We did not assess possible minor side effects of treatment. Because of known untoward effects of pentoxifylline, we looked for a possible hypotensive action of the drug by daily monitoring blood pressure, but no relevant differences were found between treatment groups.

Discussion

Drugs not previously used to treat parasitic diseases are being intensively investigated for treatment of severe and complicated malaria [26]. Several clinical and experimental studies that investigated the pathogenesis of CM have provided evidence supporting the notion that TNF is responsible for a relevant portion of the abnormalities observed in human CM [15, 16].

In this study, continuous intravenous infusion of pentoxifylline, a drug that exerts an inhibitory effect on TNF release [19], and quinine led to earlier recovery from coma by African children with CM. Those who received pentoxifylline also showed a trend toward better survival than controls who received standard quinine therapy. In accord with the supposed therapeutic mechanism of action, pentoxifylline was administered for ≤3 days, since the purpose of the study was to interfere with acute-phase phenomena, not to provide an accessory antiparasitic effect.

In the present study, ~60% of pentoxifylline recipients regained consciousness after 6 h of treatment, while slightly fewer controls did so after 46 h. Although our study was not designed to study mortality as an outcome parameter, there was a trend among the pentoxifylline-treated group toward less mortality (0 vs. 5 deaths, $P = .055$). The 16.7% mortality rate in the control group was near the median values reported by others and similar to studies with comparable disease severity on admission [1, 26]. In considering mortality, great caution is necessary, especially when results of relatively small series are considered. However, in light of the homogeneous baseline characteristics of the subjects we stud-

ied, the better survival rate recorded in children given pentoxifylline is worthy of further investigation.

We found no other relevant differences between treatment groups by other parameters used in the outcome assessment.

Although serum levels of TNF were determined for only a limited number of patients, those who received pentoxifylline tended to have decreased values on day 3 of therapy. Findings in the control group were less homogeneous: 57% had higher levels on day 3 than at admission. The ability of pentoxifylline to decrease circulating levels of TNF was also suggested by the finding in a few subjects of small increases of TNF levels after pentoxifylline was stopped. Researchers have reported dissimilar serum levels of TNF as determined by immunoradiometric assays and ELISAs [11–13]. Stratification of severity and prognosis of CM by TNF serum levels seems feasible within single series but does not appear to be appropriate in absolute terms, since values associated with mortality in one study may correspond to better outcomes in other clinical investigations.

Along with standardization of dosing methods, we should consider other factors that may substantially interfere with interpretation of clinical studies of TNF. The molecule has a short half-life in serum [7] and is produced sporadically or phasically, as shown in longitudinal studies of septic patients [27], so that peak levels may be missed and single blood samples may be misleading. Biologic effects of TNF may not depend upon circulating levels but on its production and paracrine effects in specific body sites. Furthermore, soluble receptor fragments have been identified [28], which tend to neutralize circulating TNF, and because tolerance to TNF develops [29], repeated exposure may modify the host response to TNF.

A pentoxifylline-induced decrease of TNF serum levels has been described [19, 30]; however, because different anti-TNF measures (monoclonal antibodies) provide only moderate effects on the clinical course of CM [31], other possible alternative mechanisms of action should be considered. While an additional antiparasitic effect of the drug seems improbable, we cannot rule out the hypothesis that some of the benefit of pentoxifylline seen in our study may have resulted from its recognized favorable action on capillary flow. Pathology of CM mainly consists of microcirculatory alterations [5], with parasitized erythrocytes obstructing blood flow beginning at the capillary level. One study [32] on human CM showed evidence of cerebral anaerobic glycolysis with high levels of cerebral venous Po_2, suggesting that mechanical vessel obstruction by parasitized erythrocytes may cause an imbalance in the distribution of cerebral microcirculatory flow with areas of low flow and adjacent regions of "luxury" perfusion resulting in an overall lower oxygen uptake. On this basis, it appears possible that pentoxifylline may provide some therapeutic effects through its hemorrheologic properties [33].

Our results suggest that pentoxifylline, whatever its mechanism of action, may be useful in shortening coma duration and possibly reducing mortality in children receiving conventional quinine treatment. Larger double-blind trials are required to better assess the therapeutic potential of the drug in this setting.

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