Comparison of combinations of parenteral artemisinin derivatives plus oral mefloquine with intravenous quinine plus oral tetracycline for treating cerebral malaria

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A total of 141 cases of strictly defined cerebral malaria were studied in a controlled trial of three regimens: (1) intramuscular artemether plus oral mefloquine, (2) intravenous artesunate plus oral mefloquine, and (3) intravenous quinine (with or without an initial loading dose) plus oral tetracycline. The overall mortalities in each group were 14%, 8.3% and 34.3% respectively. The average parasite clearance time was 27.30 ± 19.62 hours in regimen 1, 41.84 ± 17.55 hours in regimen 2, and 47.30 ± 21.95 hours in regimen 3. No recrudescence was observed in regimens 1 and 2, but 12.1% recrudesced in the third.

Introduction

The mortality due to strictly defined cerebral malaria, from various previous reports, has consistently remained above 20%. An increasing decline in the efficacy of standard intravenous quinine therapy in cerebral malaria has been observed by many clinicians over the past few years. Untreated severe malaria patients have been recommended to be treated with an initial loading dose of quinine (1). Cure rates are reported to be better when oral tetracycline (2) is added to the quinine course (2).

Results of clinical trials on a limited number of cases suggest that parenteral artemisinin derivatives may be superior to quinine in the treatment of cerebral malaria (3). We have ourselves experienced a very illustrative case, back in 1984 — a quinine-refractory cerebral malaria patient who recovered dramatically on changing over to intramuscular artemether. This prompted us on to a further study of 40 cases of uncomplicated falciparum malaria in 1985 which confirmed the effectiveness of intramuscular artemether (4). However, like the other workers, we also found a high recrudescence rate with a single drug regimen of intramuscular artemether in cerebral malaria.

A combination of artemisinin with mefloquine has been reported to have a beneficial effect with the reduction in recrudescences (5–7). Marked potentiating synergism has also been reported with this combination against both mefloquine-resistant and artemisinin-resistant strains of Plasmodium berghei as well as against chloroquine-resistant P. falciparum (8). Clinical reports on the efficacy of combination regimens (intravenous quinine with tetracycline and parenteral artemisinin with mefloquine in human cerebral malaria) have been made on only a limited number of patients and without any control groups. The present study was therefore performed to find out the combination that will significantly lower the mortality as well as improve the cure rate in cerebral malaria.

Study design and methods

The trial was designed as a prospective, uni-blind, controlled study to compare the efficacy of three regimens to reduce mortality and improve recrudescence rates. The duration of the study was from February 1989 to August 1991.

Site of the study

The clinical research units of the Defence Services General Hospital and No. 2 Military Hospital are situated in Yangon where there is no active transmis-
sion of malaria. The two hospitals are fairly well equipped with facilities for intensive care as well as for clinical research. Patients are admitted from all parts of Myanmar. The majority are from Kayin, Kayah and Shan States along the Myanmar–Thai border, but patients also arrive from Kachin, Rakhine and Bago Yoma areas. Cerebral malaria patients from nearby townships are brought directly to these two hospitals, but those from more distant areas are sent through field hospitals in which case they may have received some form of antimalarial therapy on the way.

About 200 cases of cerebral malaria in all forms of manifestations, with or without other severe complications, reach these two hospitals every year and the overall mortality among comatose patients is around 20%.

Patients and methods

Human cerebral malaria patients who were in a state of unrousable coma and without any other severe complications such as renal or hepatic failure were chosen for this study.

Inclusion criteria. The criteria for including patients were as follows.

(1) Males over 17 years and less than 50 years of age.

(2) Blood film positive for *P. falciparum*.

(3) Unrousable coma (Glasgow coma score, 3/15–9/15):
   - Best verbal response
     - incomprehensible
   - Best motor response
     - non-localizing (coma should persist for more than six hours after a generalized convulsion).

(4) Exclusion of other causes of coma like meningitis, encephalitis, cerebrovascular accidents, diabetic coma and epilepsy.

(5) Patients should not have received parenteral quinine or any other parenteral antimalarial drug within the past 48 hours (oral antimalarial drugs taken prior to the development of cerebral symptoms did not preclude them from the study).

Exclusion criteria. The criteria for excluding patients are given below.

(1) Those with other complications of malaria such as renal and hepatic insufficiency, pulmonary oedema and haemoglobinuria.

(2) Those with another concomitant chronic illness like diabetes mellitus, septicaemia, meningitis, en- teric fever, leptospirosis, cerebrovascular accidents, chronic epilepsy, etc.

All cases were subjected to the following examination and investigations and all data were collected in recording forms designed for the purpose.

(i) Routine patient’s identification including age, etc.

(ii) History and physical examination, including a full neurological examination and coma score chart (Glasgow coma score).

(iii) Progress noted 6 hourly until fully conscious, and then daily thereafter.

(iv) Temperature (oral) taken 6 hourly till normal for 24 hours, and then daily.

(v) Thick and thin blood films for malaria parasites, 6 hourly till negative, and then daily till day 7 and then on days 14, 21 and 28.

(vi) Lumbar puncture and cerebrospinal fluid for proteins, sugar, cell count, Gram stain and culture.

(vii) Urine for regular examination (glucose, proteins, sedimentation, etc.)

(viii) Chest X-ray.

(ix) Electrocardiograms on day 0 before treatment, then after starting treatment daily up to day 3 and on days 7, 14, 21 and 28.

(x) Blood for haemoglobin concentration and packed cell volume, white blood cell (total and differential) counts, platelet count, and reticulocyte count.

(xi) Blood for urea, creatinine, electrolytes, sugar, serum bilirubin, aspartate aminotransferase (SGOT), and alanine aminotransferase (SGPT).

(xii) Patients were weighed when consciousness was regained.

(xiii) Side-effects were obtained by enquiry using a check-list covering all symptoms.

(xiv) Patients were kept in hospital for the whole study period (28 days).

Drug regimens

Patients were screened for entry into the study at either peripheral or central hospitals. It should be noted that patients were not accepted into the study if they had had parenteral antimalarials within 48 hours of presentation. Artemether and artesunate were available only at the central hospital. Some peripheral hospitals chose to start intravenous quinine prior to referral. These patients were kept in the quinine group of the study and continued on main-
tenance doses of quinine upon arrival at the central hospital. Other patients were randomized to receive either loading doses of quinine or one of the artemisinin derivatives. During the last year of the study, patients were only randomized into the artemether or quinine groups as the shelf-life of the artesunate had expired. Thus, the control group that received quinine consisted of a portion of truly randomized patients and a portion of non-randomized, but concomitantly studied patients. A subject’s clinical status was never used in deciding drug assignment. Furthermore our past experience has shown, and data from this study support, that these two portions in the quinine group are comparable with respect to mortality and can be considered together as one common control group.

The original rationale of employing mefloquine was to prevent or lower the recrudescence rate that is well recognized after intramuscular artemether or intravenous artesunate therapy. Thus mefloquine was administered only at 48 hours. Now that evidence of synergism between these compounds is becoming stronger it may therapeutically be advantageous to administer them simultaneously.

**Regimen 1.** Intramuscular artemether 200 mg initially, followed by 100 mg 12 hourly for 4 doses (total 600 mg), plus mefloquine 1000 mg (in a single dose) orally or through a nasogastric tube at 48 hours if the patient still could not swallow.

**Regimen 2.** Intravenous artesunate infusion 120 mg at the rate of 3 ml per minute, followed by 60 mg at 12, 24 and 48 hours, plus mefloquine 1000 mg as in regimen 1.

**Regimen 3.** Intravenous quinine dihydrochloride 600 mg in a 500 ml infusion of 5% (weight/volume) dextrose in water given over 4 hours, repeated every 8 hours until the patient could take drugs orally. Then, changed to oral quinine sulfate tablets 600 mg, 8 hourly for up to 10 days (total 18 000 mg), plus tetracycline capsules 250 mg 6 hourly for 7 days (started at 48 hours orally or by nasogastric route). An initial loading dose of quinine dihydrochloride 1200 mg infusion was given to those patients who had not been taking this drug before the development of cerebral symptoms.

The microscopists examining the peripheral blood films were totally unaware of from which patients their blood slides were taken. The parameters used in the evaluation were:

- parasite clearance time (PCT): the time from initiation of therapy to the first negative blood film that remained negative for 48 hours;
- fever clearance time (FCT): the time from initiation of therapy to the time the temperature reached normal (37°C) and remained normal for 24 hours.
- time to regain consciousness: the time from initiation of therapy till the Glasgow coma score was 15/15.

**Results**

After excluding cases using the above-mentioned criteria, 141 cases remained for evaluation, 50 on regimen 1, 24 on regimen 2, and 67 on regimen 3. Their baseline characteristics are shown in Table 1. The unequal number of cases in each group was due to reasons given above. However, the outcomes of treatment in each group, measured in terms of survival, have been significantly better with either intramuscular artemether plus mefloquine or intravenous artesunate plus mefloquine than with intravenous quinine plus tetracycline.

**Side-effects**

Side-effects were defined as symptoms or signs that appeared only after drug administration. Dizziness was complained of in both groups but this may have been due to anaemia and debility. Isolated symptoms like tinnitus, nausea and hypoglycaemia occurred in a few patients in the quinine–tetracycline group. Bradycardia was observed in some patients on the intravenous artesunate plus mefloquine regimen but required no treatment. Electrocardiograms showed sinus bradycardia between 52 and 60 per min which recovered spontaneously without cardiac medications. No serious side-effects were noted in either group. The only remarkable feature seen was a hyperaemic lesion on the right shoulder and a violaceous bullous skin lesion in the right axilla of a patient on the intramuscular artemether–mefloquine regimen, which appeared on day 2 and subsided spontaneously after 7 days. This may be a concomitant isolated finding which may or may not be related to the drug regimen.

**Mortality**

There were a total of 32 deaths, 11 of which occurred within 24 hours of starting specific antimalarial drugs. They were distributed in the three treatment groups as follows: 7 (14%) in regimen 1, 2 (8.3%) in regimen 2, and 23 (34.3%) in regimen 3 (Table 2). The majority of early deaths, 7 out of 11, were in those on regimen 3.

All fatal cases were subjected, within 6 hours of death, to routine necropsy which confirmed death from cerebral malaria. The duration of coma in patients before receiving treatment was less than 48 hours.
hours in all cases, with 28 out of 32 reaching treatment centres within 24 hours of developing the coma.

While under treatment, 6 of the fatal cases whilst still alive progressed to develop one or more of the other complications such as azotemia, hepatic dysfunction, pulmonary oedema, bleeding manifestations, and cardiac dysrhythmias before dying.

Data were analysed using EPI Info, version 5.1. When comparing the effectiveness of the three regimens on mortality using the χ²-test, the difference between the artemether, the artesunate, and the quinine group was highly significant (P = 0.006). Because of this, when regimen 1 and regimen 3 were compared again it was significant (P = 0.013) with RR = 0.41 (95% CI = 0.19, 0.87). From that, the calculated value of efficacy was 0.59 (95% CI = 0.81, 0.13). When comparing regimen 2 and regimen 3 on mortality it was significant (P = 0.015) and RR = 0.24 (95% CI = 0.06, 0.95). The calculated value of efficacy was 0.76 (95% CI = 0.05, 0.95). When regimen 1 and regimen 2 were compared they were not significantly different from each other (P = 0.488).

It is interesting to note that if the control group had excluded those who were started on parenteral quinine in the peripheral hospitals (only subjects randomized to loading doses of quinine), a comparison with the artemisinin derivatives shows very similar results to those above, namely, statistically significant benefit of artesunate vs quinine (P = 0.037) and a very suggestive benefit of artemether compared with quinine (P = 0.055). This particular analysis uses more comparable groups but gives less significant results because of the smaller numbers.

**Sequelae**

In the artemisinin–mefloquine group, there was one case of strabismus due to right lateral rectus palsy in a patient who had been in coma for 3 days with no other neurological deficit. Another case of peripheral nerve injury of the right upper limb was probably due to the effect of posture while in coma before reaching the hospital.
In the quinine–tetracycline group, there were 7 cases of transient organic psychosis on recovery from coma. Convulsive seizures persisted in 1 patient and another patient had residual left-sided hemiparesis (upper motor neurone type) without any other cause to account for it, after full investigations including a CAT scan. These sequelae may be part of the disease process rather than due to the drug regimen.

Discussion

It has been increasingly recognized that *P. falciparum* strains from the south-eastern regions of Myanmar, bordering on Thailand, have been declining in their sensitivity to standard antimalarial drugs including quinine and mefloquine.

*In vitro* studies reported from the Department of Medical Research in the Ministry of Health suggest that quinine resistance of 6% (cut-off point at 256 pmol/well) and mefloquine resistance of 26% (cut-off point at 16 pmol/well) exist in this area. Clinical efficacy of these drugs, however, has been declining already for the past two years according to our own *in vivo* data. At the same time, the mortality and morbidity from severe forms of falciparum malaria have been on the rise and were probably related to this development of drug resistance.

It now seems imperative that drug regimens that will eliminate the causative parasite rapidly must be identified as a priority and applied to the clinical situation as early as possible. Our experience of deploying, out of desperation, intramuscular artemether in cases that were quinine-refractory and the highly favourable outcomes in a number of cases led to our decision to test these regimens under controlled and closely supervised research conditions. In this area of the world where the *P. falciparum* strain is highly resistant to quinine, a comparative study of quinine with artemisinin derivatives would more easily show a significant benefit with the latter. Thus, comparative trials conducted in quinine-sensitive areas, such as Africa, may reach different conclusions regarding the relative reductions in mortality. Studies are urgently needed in both quinine-sensitive and quinine-resistant areas to determine if artemisinin derivatives can decrease the mortality, but more importantly for the resistant area there is a need to evaluate regimens in preparation for even higher failure rates with quinine.

We conclude that the combination of intramuscular artemether or intravenous artesunate plus mefloquine is superior to quinine plus tetracycline in reducing the mortality and the recrudescence rate in severe cases of human cerebral malaria (in a state of unrousable coma). The group comparisons in our study are statistically significant and the efficacy of parenteral artemisinin derivatives such as intramuscular artemether will continue to be monitored (i.e., comparisons with small intravenous-quinine control groups) in order to determine the trend for the survival of cerebral malaria patients in unrousable coma.

Résumé

Accès palustre pernicieux: comparaison des associations de dérivés de l’artémisinine par voie parentérale plus méfloquine par voie orale, et de quinine par voie intraveineuse plus tétracycline par voie orale

La mortalité due aux accès palustres pernicieux chez les sujets dans un état de coma profond montre uniformément un excédent de 20% dans le sud-est de l’Asie, où l’on rapporte de plus en plus souvent une résistance de *Plasmodium falciparum* au traitement par la quinine par voie parentérale.

Une étude prospective contrôlée en simple aveugle a été effectuée sur 141 cas d’accès pernicieux strictement définis, entre février 1989 et août 1991, afin de comparer l’efficacité de deux associations, à savoir des dérivés de l’artémisinine par voie parentérale plus de la méfloquine par voie orale d’une part, et de la quinine par voie intraveineuse plus de la tétracycline par voie orale de l’autre.

On a choisi pour l’étude des hommes ayant entre 17 et 50 ans, dont les frottis sanguins montraient la présence de *P. falciparum*, et qui étaient dans un état de coma profond (stades de Glasgow 3/15 à 9/15) et ne présentaient aucune autre complication grave telle qu’insuffisance rénale ou hépatique. Aucun d’entre eux n’avait reçu de traitement antipaludique par voie parentérale au cours des 48 heures précédentes et on les a répartis au hasard en trois groupes correspondant aux trois schémas thérapeutiques suivants: 1) artéméthre par voie intramusculaire (dose totale de 600 mg en 48 heures) plus méfloquine (1000 mg au bout de 48 heures); 2) perfusion d’artésunate (dose totale de 300 mg en 48 heures) plus

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méfloquine (1000 mg au bout de 48 heures); 3) dichlorhydrate de quinine par voie intraveineuse (dose de charge initiale de 1200 mg ou dose classique de 600 mg toutes les huit heures jusqu'à ce que le malade prenne conscience) suivi par l'administration orale de sulfate de quinine (dose totale de 18 000 mg en 10 jours) plus tétracycline (gélules de 250 mg toutes les 6 heures pendant 7 jours).

La comparaison de l'efficacité de ces trois schémas a montré que les Plasmodium disparaissaient respectivement au bout de 27,3 ± 19,62 heures dans le schéma 1, de 41,84 ± 17,55 heures dans le schéma 2 et de 47,3 ± 21,95 dans le schéma 3. Il y a eu 32 décès au total, dont 11 se sont produits dans les 24 heures ayant suivi le début du traitement antipaludique. Ces décès étaient répartis dans les trois groupes de traitement comme suit: 7 décès sur 50 malades (14%) dans le groupe 1, 2 sur 24 (8,3%) dans le groupe 2) et 23 sur 67 (34,3%) dans le groupe 3. La majorité des décès précoces, c'est-à-dire 7 sur 11, sont survenus dans le groupe soumis au schéma 3.

La durée moyenne au bout de laquelle les malades ont repris conscience a été respectivement de 37,02 ± 14,71, 33,81 ± 9,37 et 42,48 ± 16,39 heures dans les trois groupes. Il n'y a eu aucune recrudescence avec les deux schémas de traitement comportant des dérivés de l'artémisinine plus de la méfloquine, mais on a observé 7 cas (12,1%) avec le schéma quinine plus tétracycline. Aucun effet secondaire grave n'a été noté dans aucun groupe.

On peut donc en conclure que l'association d'artéméther par voie intramusculaire ou d'artésunate par voie intraveineuse plus méfloquine est plus efficace que celle de quinine par voie intra-

veineuse plus tétracycline pour obtenir une diminution de la mortalité et du taux de recrudescence en cas d'accès palustre péricieux au stade de coma profond.

**References**


