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Amodiaquine treatment of uncomplicated malaria in children, in an area of chloroquine-resistant *Plasmodium falciparum* in north–central Nigeria

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The efficacy of amodiaquine against *Plasmodium falciparum* malaria was assessed in an area of confirmed chloroquine resistance in the cool, north–central plateau of Nigeria, using a 14-day protocol. The patients were all children aged <5 years of age. The drug proved highly efficacious, giving a cure 'rate' of 100% on day 14 and mean fever- and parasite-clearance times of 1.11 and 3.11 days, respectively. It was also well tolerated. Following treatment, packed-cell volumes (PCV) generally increased (65% of patients) but remained constant (12%) or even decreased (23%) in some patients; the overall improvement in PCV was not statistically significant ($P > 0.05$). The results justify the use of amodiaquine to treat *P. falciparum* malaria in those who have failed treatment with chloroquine and the second-line drugs (e.g. sulfadoxine–pyrimethamine) currently used in Nigeria. As the amodiaquine would be better employed as one part of a combination than on its own, there is a need to identify suitable partner compounds.

Malaria is a major health problem in Nigeria. The treatment of the disease in this part of sub-Saharan Africa still relies heavily on chloroquine (CQ) as the first-line drug. Sadly, CQ resistance in Nigeria has continued to increase, in geographical spread, prevalence and intensity, since its emergence in the early 1980s. Amodiaquine (AQ), a 4-aminoquinoline closely related to CQ, is often recommended as an alternative therapy in the event of CQ failure (Anon., 1989, 1990), especially when second-line drugs, such as sulfadoxine–pyrimethamine (SP) have also failed to cure the disease. In general, however, there are too few data available on the efficacy of AQ against *Plasmodium falciparum* malaria to justify this treatment policy. The need to collect such data has become imperative, especially with

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the introduction of the new Roll Back Malaria initiative (RBM), with its emphasis on evidence-based decisions and policy formulation.

During the early 1990s, the World Health Organization (WHO) withdrew AQ from its list of registered drugs for the treatment of uncomplicated malaria. This decision was the result of reports of adverse drug reactions (ADR), mainly in travellers using the drug for chemoprophylaxis. Some of these ADR, including neutropenia (Hatton *et al.*, 1986), agranulocytosis and liver damage (Neftel *et al.*, 1986), appeared serious. Others, such as nausea and vomiting (especially when AQ was ingested on an empty stomach), transient dizziness (Bruce-Chwatt *et al.*, 1986; WHO, 1996) and a decrease in systolic blood pressure (Krishna and White, 1996; Olliaro *et al.*, 1996), were less disturbing. Like CQ, but to a much lesser extent, AQ also induces pruritus in some patients (Sowunmi, 2002). Following an extensive review of the available data on AQ (Olliaro *et al.*, 1996), which confirmed that most of the adverse events were of mild to moderate severity and that the benefits of the drug far outweighed its disadvantages (particularly in endemic areas with multiple drug resistance), the WHO re-introduced AQ into its list of approved antimalarial drugs in 1996.

The main aim of the present study, conducted in Barkin Ladi, in the highlands of north–central Nigeria, was to determine the efficacy of AQ against *P. falciparum* in an area of confirmed CQ resistance. This investigation was a 'spin-off' from a multicentre study on the efficacies of CQ and SP (as first- and second-line drugs, respectively) that was jointly organized by the Nigerian Federal Ministry of Health and the RBM initiative.

SUBJECTS AND METHODS

Study Site

The study was based at the general hospital in the town of Barkin Ladi (9°31′N, 8°54′E), about 50 km from Jos, the capital of Plateau state, in north–central Nigeria. Barkin Ladi is the administrative seat of the Barkin Ladi local government area (LGA). As in many other areas on the Jos plateau, tin-mining activities in this LGA have created numerous pits that have become suitable breeding sites for various mosquito species, including some vectors of malaria.

At the time of the present study, in August–September 2002, the LGA had a estimated population of 140,548 people (projected from primary-health-care statistics for the year 2000), of whom 20% were aged <5 years. Healthcare in the LGA is provided by the general hospital (owned by Plateau state's Ministry of Health), 54 health clinics owned by the LGA, and many private facilities (a pharmacy, 20 clinics, 46 patent-medicine stores and two diagnostic laboratories). Established in about 1942, the general hospital is a 91-bed, three-ward facility with three clinicians, 59 nurses, two midwives and four technicians (who run a spacious laboratory unit).

The subjects of the present study, all children suspected to be suffering from malaria, came from all five districts forming the Barkin Ladi LGA (i.e. Fan, Foron, Gashish, Heipang and Ropp). They had presented at the general hospital, after travelling a mean (S.D.) of 10.65 (8.36) km, following an intensive community-mobilization campaign organized by the LGA.

Selection Criteria for the Subjects

The age, weight, height and packed-cell volume (PCV) of each patient were recorded. To be enrolled in the study, a patient had to fulfill 12 criteria (WHO, 1996). He or she had to be febrile (axillary temperature ≥37.5°C), to be aged 6–59 months, to be infected with *P. falciparum* but no other malarial parasite, to have at least 2000 but no more than 250,000 asexual stages/μl blood, to be able to take oral medication, and to have no concomitant illness necessitating hospitalization. Each patient enrolled also had

to be free of severe anaemia (PCV ⩾15%), severe malnutrition and febrile conditions caused by diseases other than malaria, had to be willing to attend follow-up visits for the 14-day protocol, and to have no history of antimalarial-drug ingestion in the previous 2 days [confirmed by a negative result in a Dill–Glazko urine test (Lelijveld and Kortmann, 1970)]. Children were only enrolled after their parents/guardians gave informed consent.

Patients were excluded if they could not drink or breastfeed, or if they vomited repeatedly, had a history of convulsions associated with the current illness, or were lethargic, unconscious or unable to sit or stand up.

Treatment and Evaluation

Patients who satisfied the enrolment criteria were treated with amodiaquine tablets (Medicalex Pharmaceuticals, Chiasso, Switzerland) at 25 mg/kg over 3 days, with the first tablet given on day 0. Clinical and parasitological assessments, the results of which were used to evaluate the performance of the drug, were conducted on days 1–4, 7 and 14 (after initial assessments on day 0). The day-0 PCV (recorded on presentation) were compared with those recorded on the last day of follow-up (day 14). Level of parasitaemia (parasites/μl) was estimated by counting parasites against 200 leucocytes in a thick bloodsmear and assuming that each patient had 8000 leucocytes/μl.

Ethical Considerations

Both the design of the protocol and the implementation of the study were in accordance with standard guidelines for good clinical practice (WHO, 1995). Ethical clearance was obtained from Plateau state's Ministry of Health and Hospitals Management Board and those in charge of Barkin Ladi General Hospital and Barkin Ladi LGA. Patients were free to withdraw from the study at any time.

RESULTS

The 178 febrile patients screened for enrollment were the children of farmers (67.4%), civil servants (11.2%), motor-vehicle drivers (7.9%), artisans (6.7%), clergy (3.0%), businessmen (1.0%), students (1.0%), labourers (1.0%) or those seeking employment (1.0%). When they presented they had already had fever for 1 (29%), 2 (26%), 3 (17%), 4 (6%), 5 (2%), 6 (3%), 7 (9%) or >7 (8%) days. None of the families of the patients used bed nets.

Among those screened, 71 with *P. falciparum* parasitaemias had similar day-0 PCV (%) to 55 aparasitaemic patients, with mean (S.D.) values and [ranges] of 34.0 (6.3) [20.0–48.0] and 33.1 (6.1) [18.0–45.0], respectively [$F = 1.073$, degrees of freedom (df) = 70, $P > 0.05$]; PCV were not determined for the other 52 patients. As the ranges indicate, the lowest PCV (18%) was found in a febrile but aparasitaemic patient whereas the highest (48.0%) was in a parasitaemic patient. PCV and level of parasitaemia were poorly correlated ($r = 0.137$; Fig.). The day-0 PCV indicated that 28% (18/64) of the children investigated who were aged 6–23 months and 31% (23/72) of those aged 24–59 months had mild–moderate anaemia (i.e. PCV <30%).

Most (67.4%) of the febrile children investigated were parasitaemic (Table 1). Thirty-six patients who satisfied the inclusion criteria — 19 males, with a mean (S.D.) age of 31.8 (15.8) months and a mean (S.D.) weight of 12.8 (3.2) kg, and 17 females, with a mean (S.D.) age of 30.6 (16.1) months and a mean (S.D.) weight of 11.5 (2.4) kg — were enrolled into the study. Each male and female patient received mean (S.D.) total doses of 319 (79) and 304 (72) mg AQ, respectively. The farthest travelled of the subjects, a patient from Kura Falls, 29.3 km from the hospital, stayed in the town of Barkin Ladi for the first 8 days of the study but was then lost to follow-up.

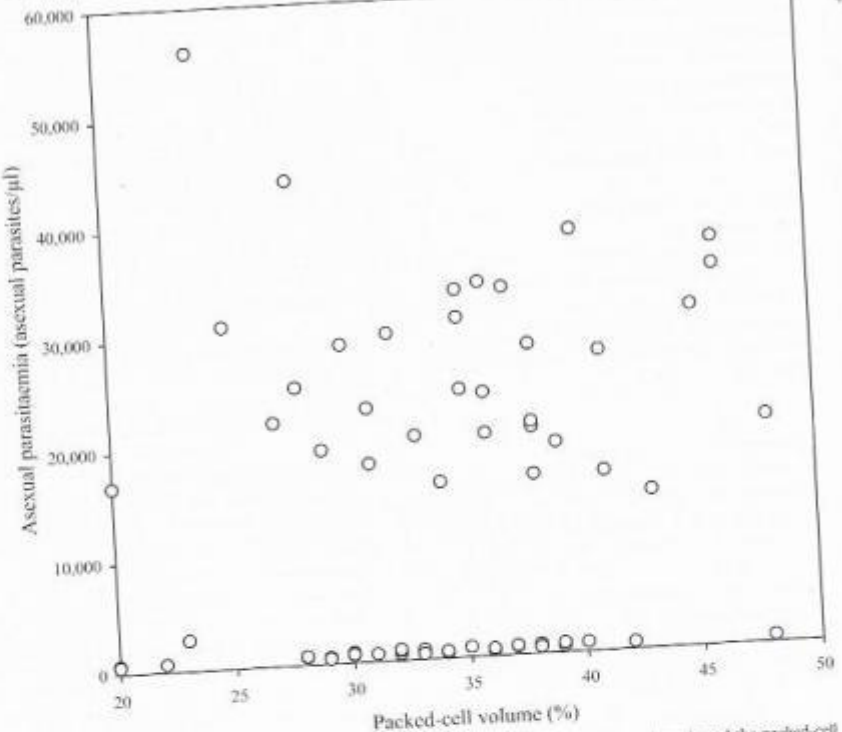

FIG. A scatterplot showing the low level of correlation between the level of asexual parasitaemia and the packed-cell volume, measured, pre-treatment, in 71 parasitaemic children with *Plasmodium falciparum* malaria.

TABLE 1. *Demographic data on the 178 febrile children screened for enrolment*

Parameter	Value
NO. AND (%) OF SUBJECTS SCREENED	
Male	98 (55)
Female	80 (45)
Positive for *Plasmodium* infection	102 (57)
Enrolled	56 (20)
MEAN VALUE, (S.D.) AND [RANGE] FOR ENROLLED PATIENT:	
Age (months)	31.2 (15.7) [6–59]
Weight (kg)	12.2 (2.9) [7.5–21.0]
Amodiaquine consumed (mg)	303.5 (71.7) [188–525]
Height (cm)	82.5 (12.4) [63.5–110.0]

Treatment with AQ led to rapid clearance of parasitaemia (Table 2), most patients (67%) being aparasitaemic by day 3 and only three (8%) remaining parasitaemic on day 4. As no parasitological failures were observed, the day-14 cure 'rate' was 100%. The mean parasite-clearance time (PCT) was 3.1 days.

Fever cleared even more rapidly than parasitaemia, with a mean fever-clearance time (FCT) of just 1.1 days (Table 3). Thirty-three (92%) of the patients were afebrile by day 1 and remained afebrile until at least day 14. One patient who had fever on day 4 and another who was febrile on day 7 appeared aparasitaemic at those times; both were later confirmed to have upper respiratory infections (that were treated appropriately at the expense of the project).

The mean (S.D.) PCV (%) recorded on day 14 was virtually the same as the baseline value on day 0 [34.87 (4.90) *v.* 34.43 (6.19)], indicating no significant improvement in this haematological parameter over the study period [$t = 1.59$; df = 34; $P > 0.05$]. The baseline PCV ranged from 23%–48% and the day-14 from 20%–42%. Between days 0 and 14, PCV (%) increased — by a mean (S.D.) and [range] of 5.1 (4.1) [2–16] — in 22 (65%) of the patients, remained unchanged in four (12%), and decreased — by a mean, (S.D.) and [range] of 5.5 (4.0) [2–13] — in eight (23%). (Follow-up data on PCV were not available for two of the enrolled patients.)

Most patients appeared well within 24–48 h of commencing AQ treatment and the only

TABLE 2. *Changes in the asexual parasitaemias of the 36 patients who were treated with amodiaquine on days 0, 1 and 2*

Day	No. of patients	Asexual parasitaemia: Geometric mean (asexual parasites/μl)	Decrease %	Range (asexual parasites/μl)
0	36	25,660	–	2786–56,400
1	36	8955	65.1	0–91,478
2	36	545	97.9	0–16,318
3	36	221	99.1	0–2263
4	36	181	99.3	0–313
7	36	0	100	0
14	35*	0	100	0

*One patient relocated out of the study area and was lost to follow-up on day 8.

TABLE 3. *Fever clearance, following treatment of* Plasmodium falciparum *malaria with amodiaquine on days 0, 1 and 2*

Day	No. of patients*	No. and (%) febrile	Axillary temperature (°C): Mean and (S.D.)	Range
0	36	36 (100)	38.9 (1.1)	37.5–40.9
1	36	3 (8)	36.8 (0.7)	35.6–38.7
2	35	1 (3)	36.4 (0.5)	35.3–37.5
3	36	0 (0)	36.3 (0.5)	35.1–36.9
4	34	1 (3)†	36.5 (0.4)	35.7–37.7
7	36	1 (3)†	36.5 (0.5)	35.6–37.7
14	35	0 (0)	36.7 (0.5)	35.0–37.3

*One patient relocated out of study area on day 8, and temperature data for the other 35 patients were not complete.
†Apparently aparasitaemic.

adverse reaction observed was mild pruritus recorded in one child following ingestion of the drug on days 1 and 2.

DISCUSSION

The results of the present assessment of the performance of AQ in the treatment of uncomplicated, *P. falciparum* malaria in north–central Nigeria demonstrate the drug's very high efficacy. This finding is significant for a number of reasons. Firstly, it provides the necessary evidence and justification for the national policy of using AQ as alternative therapy where CQ (or even second-line drugs such as SP) has proven ineffective against *P. falciparum* malaria. Secondly, compared with the artemisinin derivatives (dihydroartemisinin, artesunate, artemether) and several drug combinations that are currently available in Nigeria, AQ is a relatively cheap alternative drug and much more affordable to the vast majority of potential users, especially those living in less affluent, rural communities. Thirdly, the data demonstrate the potential role of AQ in reducing malaria-related morbidity and mortality — a major objective of the primary-health-care programme in Nigeria. There is ample evidence, from Nigeria and other parts of tropical Africa, that CQ resistance is increasing such morbidity and mortality. For example, Asindi *et al.* (1993) noted an increase in the incidence of convulsions and cerebral malaria in children in south–eastern Nigeria and found this trend to correspond to the emergence of CQ resistance in the area. Severe malarial anaemia appears to be particularly common in areas with high prevalences and levels of CQ resistance (Brewster and Greenwood, 1993). Some of the malaria-attributable mortality in Africa may be due to ineffective CQ chemoprophylaxis during pregnancy. There is certainly much evidence to support the proposition that malaria-treatment policies in Africa generally need to be changed (Bloland *et al.*, 1993; Trape, 1999).

Fleming and Werblińska (1982) reviewed the prevalence of anaemia among children in some West African countries; the levels varied from 38% in Cameroon to 59% in Togo, 62% in Liberia and 63% in Nigeria. Although the aetiology of the childhood anaemia in Nigeria was always multiple (including viral or bacterial infections, sideropenia, folate deficiency, hypoproteinaemia and sickle-cell disease), 62% of the cases of anaemia were associated with malaria (Fleming and Werblińska, 1982). These records, however, pre-date the emergence and widespread occurrence of antimalarial resistance in most parts of the region. It would be interesting to re-evaluate the anaemia situation now, under the current intensification of resistance.

Impressive as the performance of AQ was against *P. falciparum* malaria in the north–central area of Nigeria (present study), it is necessary to begin to explore mechanisms for ensuring the prolonged useful therapeutic life of this drug. Observations made on the Kenyan coast, where the cure 'rate' with AQ fell from 98% in 1983 to 96% in 1988, 75% in 1990, and about 70% in 1993 (W. M. Watkins, unpubl. obs.), underscore this point. A possible strategy is one in which AQ is combined with a suitable antimalarial drug of proven efficacy (White, 1999). Appropriate candidates for the mixture are unrelated compounds with different pharmacological action, including the artemisinin derivatives and sulfonamides.

AQ appears to be well tolerated by Nigerian children living on the central plateau. The observed prevalence of pruritus following AQ (3%) is lower than that observed following CQ in the same area (unpubl. obs.). Given the clinical history of AQ, however, there is still a clear need to monitor carefully for more serious adverse effects, as use of AQ to treat *P. falciparum* strains that are resistant to CQ and/or second-line drugs becomes more common. Mechanisms for reversing antimalarial drug resistance should continue to be investigated, and the criteria for changing from one drug (against which parasites have become resistant) to a more effective therapy should be clearly defined.

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