



Amodiaquine alone, amodiaquine + sulphadoxine-pyrimethamine, amodiaquine + artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian children: a four-arm randomized effectiveness trial

CITATION

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RESEARCH QUESTION

How effective are the three drug combinations (amodiaquine + sulphadoxine-pyrimethamine, amodiaquine + artesunate, and artemether-lumefantrine) that have proven efficacy in east Africa, in a real world situation (clinic setting in which drugs are dispensed and taken at home unobserved by medical staff) compared to the current amodiaquine monotherapy?

THE STUDY DESIGN

Randomised, open label, controlled trial

STUDY SETTING

Outpatient clinic of Teule Hospital, Muheza, Tanzania (high drug resistance area) Written informed consent; Ethics approval obtained
July 2002-September 2002: Pilot study
September 2002-October 2004: main study

PARTICIPANTS

Included:

Children aged 4–59 months, with symptoms suggestive of clinical malaria and *P falciparum* parasitaemia of at least 2000 parasites per μL of blood, were able to take study drugs by the oral route, were able to attend clinic on stipulated days for follow-up, and if a parent or guardian provided written informed consent for the child to participate in the study.

Excluded:

Presence of severe and complicated malaria as defined by WHO; a mixed *plasmodial* infection, or concomitant disease masking assessment of the response to antimalarial treatment; intake of antimalarials other than chloroquine within the past 7 days; and known hypersensitivity to any of the study drugs.

INTERVENTIONS

Initial Pilot Study: Children were randomised to receive sulfadoxine-pyrimethamine (1.25 mg/kg pyrimethamine and 25 mg/kg sulfadoxine), given as a single dose or amodiaquine (25 mg/kg) given over 3 days (10 mg/kg on each of the first 2 days and 5 mg/kg on the third day).

Main Study: Children were randomised to receive amodiaquine (Sanofi), amodiaquine+sulfadoxine-pyrimethamine (Roche), artemether-lumefantrine (co-artemether, Novartis), or amodiaquine+artesunate (Sanofi; 4 mg/kg artesunate given for 3 days)

OUTCOMES

The primary endpoint: parasitological failure by day 14 assessed blind to treatment allocation.

Secondary endpoints: parasitological failure by day 28 and gametocyte carriage (days 14 and 28).

RISK OF BIAS (Risk Scale: Low-Moderate-High)

SELECTION BIAS: Low

Allocation sequence was generated by computer (Stata version 6), with blocks of variable sizes. Treatment allocations were put into opaque, sealed and countersigned, sequentially numbered envelopes. Opening the envelope defined entry to the trial; subsequent intention-to-treat analysis was undertaken on the basis of treatment allocation. Baseline characteristics comparable across the four groups.

PERFORMANCE BIAS: Moderate

Open –label study. Controlled effectiveness trial with amodiaquine as control treatment regimen. Treatment was self administered.

DETECTION BIAS: Moderate

Investigators were aware of treatment assignment but the Laboratory staff were blinded. Laboratory staff were blinded.

ATTRITION BIAS: Low

Analysis was by intention to treat principle. Loss to follow up was low for an effectiveness study (78 were lost to follow up out of 1811 randomised, <5%).

STUDY FINDINGS:

(Refer to study profile: figure 1)

Of 3,158 children screened, 1,811 were randomly assigned treatment and 1,717 (95%) reached the 14-day follow-up. The amodiaquine group was stopped early by the data and safety monitoring board because it reached a pre-determined stopping rule of more than 40% parasitological failure by day 14.

Primary endpoint: Day 14 parasitological failure rates were 103 of 248 (42%) for amodiaquine, 97 of 476 (20%) for amodiaquine+sulfadoxine-pyrimethamine, 54 of 491 (11%) for amodiaquine+artesunate, and seven of 502 (1%) for artemether-lumefantrine.

Secondary endpoint: Day 28 parasitological failure rates were 182 of 239 (76%), 282 of 476 (61%), 193 of 472 (40%), and 103 of 485 (21%), respectively. The difference between individual treatment groups and the next best treatment combination was significant (p0.001) in every case. Recrudescence rates by day 28, after correction by genotyping, were 48.4%, 34.5%, 11.2%, and 2.8%, respectively.

Gametocyte carriage:

There were substantially fewer gametocytes at day 14 in the two artemisinin-containing combination groups than in the amodiaquine+sulfadoxine-pyrimethamine combination group (table 2). Additionally, gametocyte prevalence at day 14 in the artemisinin groups was significantly reduced from that recorded at patient presentation (117 of 556 [21%, 95% CI 18–25])

ADVERSE EVENTS

Three patients died during this study. One child in the amodiaquine and sulfadoxine-pyrimethamine group died on the day of randomisation and one in the amodiaquine group died 2 days after randomisation. The third child in the artemether-lumefantrine group died on day 20 at home, having been well and parasite free on day 14. One other serious adverse event was recorded, a child who required hospitalisation for a rash on day 20.

COMMENTS:

The results showed that the six-dose regimen of artemether-lumefantrine is more effective than the amodiaquine + sulphadoxine-pyrimethamine, amodiaquine + artesunate combinations. The study also shows that combinations of artemisinin with failing drugs in the region (ie, amodiaquine and sulfadoxine-pyrimethamine) is less effective.

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