



Audiometric changes associated with the treatment of uncomplicated falciparum malaria with co-artemether

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Summary Animal studies have demonstrated artemisinin brain stem toxicity with auditory centres being especially affected; there has, to date, been no evidence of such toxicity with oral artemesinins in humans. Subjects working at a construction site in Mozambique had audiometric assessments taken on joining and leaving the project. Subjects with uncomplicated malaras received co-artemether (artemether–lumefantrine) ($n = 150$) while age-, gender-, weight- and race-matched controls ($n = 150$) neither suffered malaria nor received antimalarial therapy. Hearing thresholds were measured at predefined frequencies in treated subjects and controls. Subjects receiving co-artemether had a significantly greater hearing loss than controls at all frequencies except 250 Hz and 500 Hz (P values ranging from <0.001 to 0.04 , Mann–Whitney U). Mean changes at the different frequencies in subjects ranged from -6.50 dB (95% CI -8.19 to -4.81) [at 1 kHz frequency] to -0.07 dB (95% CI -2.19 to 2.05) [at 6 kHz frequency]. Mean changes in the control group ranged from -4.20 dB (95% CI -5.97 to -2.43) [at 1 kHz frequency] to $+2.7$ dB (95% CI -0.93 to 4.47) [at 6 kHz frequency]. Treatment of uncomplicated malaria with co-artemether is associated with hearing loss, possibly from synergy between potentially ototoxic agents in combination. The safety and neurotoxicity of artemesinins and other endoperoxides needs to be more fully evaluated.

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1. Introduction

Clinical experience with artemesinins has shown them to be the most rapidly acting antimalarials available (White and Olliaro, 1998). Their use in areas where widespread resistance by *Plasmodium falciparum* threatened to render falciparum malaria untreatable may well have averted

a 'malaria disaster' (White et al., 1999a). The artemesinins have been viewed as a critical intervention in the fight against malaria by some authors, and these agents have assumed a central role in the global effort to roll back malaria (White, 1999; White et al., 1999a).

As a group, artemesinins are characterized by an extremely short half-life, which has the potential to permit recrudescence of malaria unless patients complete a full 7 d course of treatment. This problem, and a desire to avoid the emergence of resistance, has led to the recommendation

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that artemisinins should be used in combination with a second antimalarial, a strategy labelled 'artemisinin combination therapy' (ACT) (White and Olliaro, 1998; White et al., 1999a). The co-formulation of artemether in fixed combination with lumefantrine is known as co-artemether, and reflects this thinking.

Lumefantrine, the second antimalarial contained in co-artemether, is a synthetic antimalarial chemically related to halofantrine and mefloquine. Lumefantrine has an elimination half-life of up to 6 d in malaria patients, and is intended to eradicate parasites not killed by the faster acting artemether (White et al., 1999b). Co-artemether is typically administered in six doses over 3 d, giving a total adult dose of 480 mg of artemether and 2880 mg of lumefantrine.

Concerns have been expressed that these compounds may be neurotoxic in humans (Hoffman, 1996; Miller and Panosian, 1997). Animal studies have shown that high dose parenteral administration of the lipophilic artemisinin molecules artemether and arteether results in the development of focal brain stem lesions, with pathways involved in auditory processing being particularly affected (Nontprasert et al., 2002a,b). Similar brain stem toxicity findings have been observed after parenteral administration in rodents, canines, and monkeys administered artemether or arteether intramuscularly. Toxicity was evidenced by disturbances of gait, diminution of spinal, brain stem and pain reflexes, and eventually death (Brewer et al., 1994a,b; Dayan, 1998; Nontprasert, 2002a). Despite this, no signs of neurotoxicity have been observed in humans treated with artemisinins (Price et al., 1999). This lack of observed toxicity has been explained on pharmacokinetic grounds, with lack of accumulation attributed to the extremely short half-life offered as an explanation; animal experimentation utilizing oral and parenteral administration is cited in support (Nontprasert et al., 1998, 2000). The logic underlying this argument is that while sustained exposure to artemisinins may prove neurotoxic, intermittent brief exposure, as occurs with oral administration, will not give artemisinins an opportunity to effect neuronal harm.

A pivotal retrospective study in the clinical development of co-artemether compared the post-exposure audiograms and brain stem auditory evoked responses (BAERs) of 79 human subjects, treated with at least two courses of various forms of artemisinin or ACT, to those of 79 age- and gender-matched controls who had never received an artemisinin (van Vugt et al., 2000). The study failed to reveal any significant difference between the audiograms and BAERs of subjects and con-

trols. No audiograms were taken pre-treatment in the study group however, and thus no assessment of individual subjects' hearing loss could be made. A similar but larger study in Viet Nam reached the same conclusions (Kissinger et al., 2000). The artemisinin compound that subjects received in these studies were not standardized, with lipophilic and water-soluble compounds being variously administered.

We therefore undertook a follow-up study. Audiograms were collected from employees when they were first employed at a construction site in Mozambique; this was repeated at the termination of contract. We then compared audiometric data from subjects who received only co-artemether with those who were not exposed to the drug. No other artemisinins were used in these employees.

2. Materials and methods

The data was collected within the framework of a routine care setting at a construction site of approximately 120 ha in Mozambique, from 1 July 2001 to 30 April 2003. Subjects gave their informed consent. All employees were required to have a physical examination that included an audiogram as part of their induction. Subjects judged to be suffering from serious hearing loss, as shown by two separate audiograms, were denied employment and consequently not included in the study. Similarly, potential employees found to be suffering from serious physical conditions were denied employment. Serological testing for HIV infection did not form part of the baseline examination.

All employees were required to undergo a similar physical examination and have an audiogram taken upon completing their term of employment on the project.

The authors were the sole providers of medical care to the construction project and adopted a defined malaria treatment protocol. This protocol called for the ambulatory use of co-artemether in the treatment of uncomplicated malaria. No other antimalarials were used to treat uncomplicated malaria cases. Malaria was adjudged complicated by reference to a set of modified WHO criteria, and all cases of complicated malaria were excluded from this study (WHO, 2000). These criteria were modified because urea, electrolyte, and liver function testing were not readily available. These parameters were crudely assessed clinically with routine urinalysis undertaken. Our clinical success with use of these amended criteria in combination with co-artemether for the treatment of falciparum

malaria has been reported elsewhere (Toovey and Jamieson, 2002).

Air conduction audiometry was undertaken using the following audiometers: Interacoustics AS 208 (Inetracoustics, Denmark); Welch Allyn AM 232 (Welch Allyn, USA); and Grayson Stadler GSI-17 (Viasys, USA). All audiometers were calibrated by an external agency in accordance with the manufacturers' recommendations. Audiometrists were blinded during the exit audiogram as to whether subjects belonged to the treatment or control group.

The hearing threshold was measured and recorded at the following frequencies for each ear in turn: 250 Hz, 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, and 8 kHz. The hearing threshold change for each subject at each measured frequency was calculated by subtracting the hearing threshold measurement obtained at the end of the subject's term of duty from that obtained on entry.

A total of 150 subjects who had received co-artemether (Novartis, Basel, Switzerland) were available for inclusion in the data analysis. These were individuals for whom complete pre- and post-employment audiograms were available. A control group of 150 subjects, employed at the same site and who had not suffered from malaria or received any treatment for malaria during their employment, was drawn from the same medical records database. The control subjects were drawn in sequential date order from the database, based upon the date of their first audiograms.

Data and measurements were entered into an Excel spreadsheet and analysed using plug-in statistical software (Analyse-It, version 1.68).

3. Results

The treatment and control groups exhibited no significant differences in terms of age, gender, mass, and race. Specifically, 146 of the treatment subjects were Negroid males, two were Negroid females, and two were Caucasian males. The racial and gender composition of the control group was almost identical, comprising 147 Negroid males, two Negroid females, and one Caucasian male. More than 95% of subjects in both the treatment and control groups were labourers or artisans who worked at the same noise level.

Ages were available for 148 of the treatment group and all 150 of the control group. A Mann–Whitney *U* test (two-tailed) comparing the age distributions in the two groups was performed and no statistically significant difference was found ($P = 0.66$). The median age in the treat-

ment group was 29 years (range 19–65 years, 95% CI 27.0–31.0). In the control group the median age was 29.5 years (range 18–72 years, 95% CI 28.0–32.0).

Weights were available for all subjects in both the treatment and control groups and were comparable between these two groups. A *P*-value of 0.76 was obtained for the comparison of the means using a two-tailed Mann–Whitney *U* test. The median weight for the treatment group was 62.0 kg (range 43–102 kg, 95% CI 61.0–64.0). The corresponding median weight for the control group was 62.0 kg (range 47–95 kg, 95% CI 60.0–64.0).

The mean interval between initiation of treatment with co-artemether and the taking of the post-exposure audiogram in treatment subjects was 163.8 d (range 3–392 d, SD = 91.91); the median interval was 159.95 d.

Sixteen hearing threshold determinations were measured in each subject during employment and termination audiograms, representing eight determinations per side for each audiogram. The hearing threshold change was then calculated, with a negative result indicating a net hearing loss at a particular measured frequency. The mean threshold change was negative at all 16 threshold determinations in the treatment group, ranging from -6.50 dB (95% CI -8.19 to -4.81) to -0.07 dB (95% CI -2.19 to 2.05). Mean threshold changes in controls ranged from $+2.7$ dB (95% CI -0.93 to 4.47) to -4.20 dB (95% CI -5.97 to -2.43), and were negative in nine of the 16 threshold determinations.

Hearing threshold loss was significantly greater in the treatment group than in the control group at all except the very lowest frequencies, 250 Hz and 500 Hz (Figure 1).

The decibel loss for each frequency determination in the treatment and control groups and corresponding *P* values are shown in Table 1. At the 8, 6, 4, 3, 2, and 1 kHz frequencies, differences between the treatment and control groups were significant. Although the magnitude of the hearing loss was most pronounced at the 1 kHz frequency, differences between the median losses of treatment and control subjects were greatest at frequencies from 2 kHz upwards. At the lower frequencies of 500 Hz and 250 Hz, the differences between the treatment and control groups were not statistically significant.

4. Discussion

It is well known that antimalarials may be ototoxic, with quinine's ototoxic effects ensconced in the medical lexicon under their own singular name, cinchonism. Neurotoxicity and ototoxicity

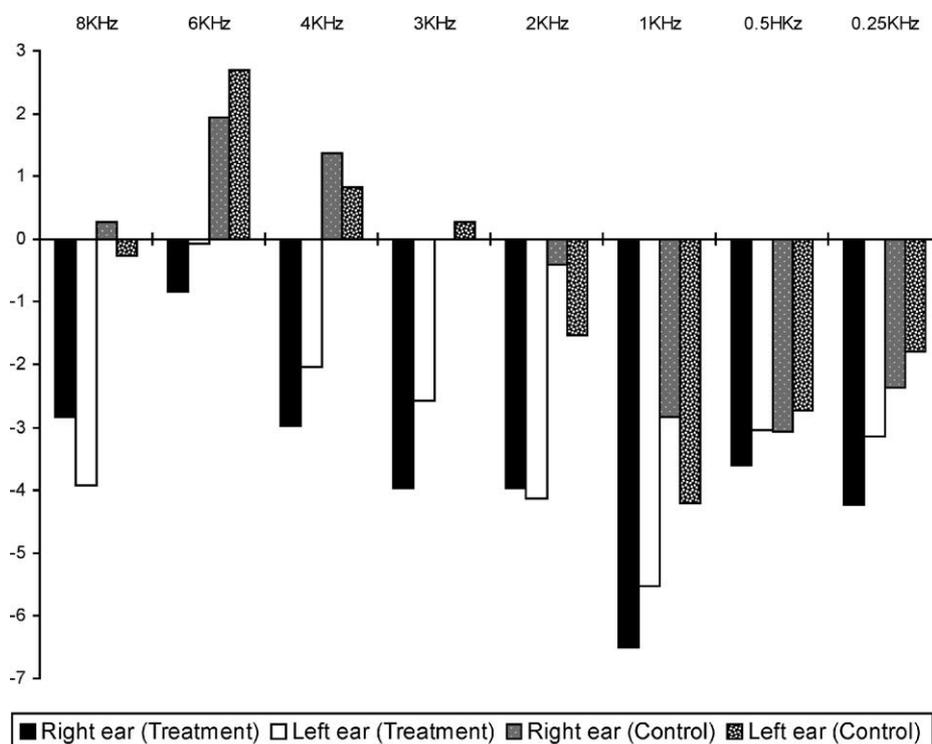


Figure 1 Mean net hearing loss (dB), measured as difference between pre- and post-project assessment, in co-artemether exposed subjects and controls. Negative values reflect a hearing loss.

have been reported with antimalarials other than quinine, with case reports implicating mefloquine and chloroquine (Claessen et al., 1998; Fusetti et al., 1999; Hadi et al., 1996; Phillips-Howard and ter Kuile, 1995).

The development of cinchonism in patients in the absence of malaria is documented, e.g. in patients treated with quinine for babesiosis (Krause et al., 2000; Roche et al., 1990; Tange et al., 1997). While quinine, mefloquine, and chloroquine are chemically related, it seems an unusual coincidence that the unrelated artemisinins should exhibit ototoxicity. It has been suggested that the ototoxicity of antimalarials may have a common pathway, involving the exposure of auditory neurones to heme, although the appearance of cinchonism in healthy volunteers and babesiosis patients calls this in to question. While the exact antiplasmodial action of the artemisinins remains unresolved, it is postulated that the opening of the endoperoxide bridge shared by all artemisinins results in the generation of free radicals that fatally damage the parasite (Cumming et al., 1997; Meshnick et al., 1996). Such a mechanism of action could potentially expose neurones to heme and result in ototoxicity, but the neurotoxicity evident in animal models operates in the absence of plasmodial infection, and human ototoxicity may operate as a direct drug effect rather than through the mediation of malaria.

It is known that malaria itself can cause harm to hearing, with hearing loss being a recognized complication of cerebral malaria (Sowunmi, 1997). All of our patients were classified as suffering from uncomplicated malaria however, and all were treated on an ambulatory outpatient basis. Studies of the hearing loss attributed to quinine during malaria treatment show the loss to be reversible, pointing to drug rather than disease as the cause (Berninger et al., 1998; Karbwang et al., 1994; Karlsson et al., 1994; Roche et al., 1990; White, 2000). The negative hearing threshold changes in nine of the sixteen determinations in the control group are thought most likely due to noise exposure during construction work.

It remains an open question whether the ototoxicity seen in our subjects can be attributed to the artemether component of co-artemether, to the lumefantrine component, the combination of the two, or even to malaria itself. An additional possibility is that ototoxicity inherent in co-artemether may have been potentiated by occupational noise exposure. Lumefantrine is chemically related to mefloquine and it is therefore not inconceivable that it may possess some of mefloquine's neuro- and oto-toxicity. The combination of two possibly ototoxic agents, artemether and lumefantrine, in a single formulation might also explain the ototoxicity we have

Table 1 Comparison between co-artemether exposed subjects and controls showing median decibel loss, interquartile range, and *P*-values (Mann–Whitney *U* single-tail)

Frequency	Side	Exposed to drug?	Median (dB)	95% CI of median	IQR	<i>P</i> -value
8 kHz	R	Y	−5	−5.00 to 0.00	20.00	0.01
		N	0	−5.00 to 0.00	20.00	
	L	Y	−5	−10.00 to 0.00	20.00	<0.01
		N	0	−5.00 to 5.00	16.25	
6 kHz	R	Y	0	−5.00 to 5.00	15.00	0.03
		N	0	0.00 to 5.00	15.00	
	L	Y	0	−5.00 to 0.00	10.00	0.01
		N	5	0.00 to 5.00	15.00	
4 kHz	R	Y	−5	−5.00 to 0.00	15.00	<0.001
		N	0	0.00 to 5.00	15.00	
	L	Y	−5	−5.00 to 0.00	15.00	<0.01
		N	0	0.00 to 5.00	15.00	
3 kHz	R	Y	−5	−10.00 to 0.00	15.00	<0.001
		N	0	0.00 to 5.00	18.75	
	L	Y	−2.5	−5.00 to 0.00	15.00	<0.01
		N	0	0.00 to 0.00	15.00	
2 kHz	R	Y	−5	−10.00 to −5.00	15.00	<0.01
		N	0	−5.00 to 5.00	16.00	
	L	Y	−5	−5.00 to −5.00	10.00	<0.01
		N	0	−5.00 to 0.00	15.00	
1 kHz	R	Y	−5	−10.00 to −5.00	15.00	<0.01
		N	−2.5	−5.00 to 0.00	15.00	
	L	Y	−7.5	−10.00 to −5.00	13.75	0.04
		N	−5	−5.00 to 0.00	15.00	
500 Hz	R	Y	−5	−10.00 to 0.00	15.00	NS
		N	−5	−5.00 to 0.00	15.00	
	L	Y	−5	−5.00 to 0.00	15.00	NS
		N	−5	−5.00 to 0.00	15.00	
250 Hz	R	Y	−5	−5.00 to −5.00	11.25	NS
		N	−2.5	−5.00 to 0.00	15.00	
	L	Y	−5	−5.00 to 0.00	10.00	NS
		N	0	−5.00 to 0.00	15.00	

seen, with each agent potentiating the other's ototoxicity.

Given the known oto- and neuro-toxicity of the lipophilic artemisinins (artemether and arteether) there are reasonable grounds to suspect the artemether component of co-artemether as responsible (Brewer et al., 1994a,b; Genovese et al., 2000; White, 2000), although on theoretical grounds at least lumefantrine might also be expected to have ototoxic potential. On the other hand, a recent study of the brain stems of subjects that had died from severe malaria failed to detect any neurohistological difference between those treated with artemether ($n = 6$) and those treated with quinine ($n = 15$) (Hien et al., 2003). Similarly,

no damage to the central nervous system was seen in rats exposed to repeated high doses (400 mg/kg) of oral artemether (Xiao et al., 2002b). The nature of the changes that artemether might induce neuronally may however be at the molecular and functional level, and thus not be always visible histologically.

It has been suggested that assessments of tempero-spatial sound discrimination might be a more sensitive indicator of thalamic and cortical auditory neurotoxicity than measurement of auditory evoked responses, and that this might more readily detect oto- and neuro-toxicity (van Vugt et al., 2000). The assessment of intra-individual, as opposed to inter-individual, threshold changes and

their comparison with a control group has nevertheless revealed a small but consistent hearing loss in subjects treated for malaria with co-artemether, at all but the very lowest frequencies. The lengthy duration (mean 163.8 d, range 3–392 d, SD 91.91) in most subjects between exposure to co-artemether and measurement of the post-exposure audiogram makes the hearing loss demonstrated appear irreversible.

The implications of finding the artemisinins, or at least artemether, to be most likely irreversibly ototoxic could be very significant. Recent work has demonstrated that the artemisinins exhibit antischistosomal activity, and it is possible that their role may be expanded to include the treatment and prophylaxis of schistosomiasis (Utzinger et al., 2001, 2002; Xiao et al., 2002a). Demonstration of neurotoxicity may impede their deployment in this role as well as in the treatment of malaria.

The finding of audiometric changes raises the question of what other neurotoxic effects the artemisinins may possess, and whether these will manifest at a later stage in exposed subjects. Neurotoxicity should particularly be evaluated in children, as the susceptibility of the developing nervous system to insult could be greater than in adults. This may be of particular concern in endemic areas, where frequent treatment with anti-malarials raises the possibility that toxicity might be cumulative. Since animal studies have shown the lipophilic arteether to be neurotoxic, when compared to the more water soluble artesunate and artelinate, additional prospective studies are needed with such agents (Genovese et al., 2000).

5. Conflicts of interest statement

The authors received no financial support for this work. The authors have been reimbursed by Novartis for speaking and attending conferences. One of the authors has a close personal relationship with a Novartis employee previously associated with co-artemether.

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