Quinine induces reversible high-tone hearing loss

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Serial audiometry was performed in ten patients receiving quinine treatment for acute falciparum malaria. Quinine reduced high tone auditory acuity in all patients, resulting in flattening of the audiograms. The effect was rapid in onset, usually unnoticed (although tinnitus was reported in seven patients), and resolved completely after treatment was completed.

Keywords quinine deafness toxicity

Introduction

The cinchona alkaloids are still widely used both as pharmaceuticals and food flavourings. Quinidine is prescribed as an antiarrhythmic drug in cardiovascular medicine. Quinine, the laevorotatory diastereomer of quinidine, is used as an antimalarial, in the prevention of night cramps, and as a bittering agent (particularly in Indian tonic water). It has a narrow therapeutic ratio (White, 1988). Plasma concentrations exceeding 5 mg l⁻¹ are usual in the treatment of malaria and are associated with a characteristic symptom complex comprising tinnitus, nausea, dysphoria and deafness which is known as 'cinchonism' (Powell & McNamara, 1964). The hearing loss induced by quinine has not been characterised previously.

Methods

Ten adult patients with acute falciparum malaria were studied. Three patients were considered to require parenteral treatment because of vomiting, and were given an initial intravenous loading dose (20 mg salt kg⁻¹) of quinine dihydrochloride. The remainder were treated with oral quinine sulphate 10 mg salt kg⁻¹ three times daily and tetracycline 250 mg four times daily for

1 week. Patients were excluded if they had previous hearing abnormalities, were receiving other drugs known to affect hearing (salicylates, aminoglycosides etc), or were uncooperative. All gave fully informed consent to the testing and sampling procedures. On admission baseline blood samples were taken for quantitative parasite count, full blood count, biochemical screen, and baseline quinine level. Before treatment a symptom questionnaire was completed and baseline audiometry was performed in triplicate, at intervals of 10 min. Audiometry was performed in an ordinary non-soundproofed hospital side-room at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6 and 8 kHz using a portable screening audiometer (Kamplex A57). The symptom questionnaire was completed, audiometry was repeated, and plasma quinine levels were taken at 1, 2, 3, 4 and 5 h after starting treatment and then daily, before and after the first treatment dose of the day until discharge, and again more than 48 h after completing the course of quinine treatment. Vital signs were measured four hourly and parasite counts were checked twice daily. Quinine was measured by high performance liquid chromatography with fluorescence detection and plasma protein binding was determined as described previously (Silamut *et al.*, 1985).

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Results

Toxicity

All patients recovered without complications. Three of the ten patients vomited within 4 h of the first dose, and two others complained of nausea. Two of the seven patients on oral treatment developed symptomatic postural hypotension. Tinnitus developed in seven patients a median of 3 h (range 1–24) after starting treatment. Headache usually improved with reduction in fever. Abdominal pain appeared unrelated to quinine, and no patient complained of disturbed vision. Only one patient was aware of any hearing loss but this recovered when he stopped taking quinine.

Audiometry

Hearing loss was evident in all patients following the first dose of quinine, and was greatest at the higher frequencies (Figure 1). This resulted in flattening of the audiograms. The reduction in auditory acuity followed the rise in plasma quinine concentrations suggesting a lag phase in equilibrating between plasma and the cochlear apparatus. Tinnitus began after plasma concentrations exceeded 5 mg l^{-1} . Hearing loss persisted unchanged on the second and third day

and had improved on the fourth day of treatment as plasma concentrations of quinine declined. At follow up, audiograms had returned to baseline values at all frequencies. There was a consistent further reduction in auditory acuity [mean ($\pm$ s.d.) $13 \pm 2 \text{ dB}$] following oral administration of quinine on days 2, 3 and 4. This was also greatest at the highest frequency tested (8 kHz).

Plasma quinine concentrations

In the seven patients treated with oral quinine, peak plasma concentrations occurred a median of 3 h (range 1–4 h) after starting treatment. Overall peak concentrations ($n = 10$) ranged from 3.8 to 21 mg l^{-1} . Mean (s.d.) plasma protein binding was $94.0 \pm 2.5\%$. The mean (s.d.) increment in plasma concentrations on subsequent days following the first dose of the day was 2.2 (2.1) mg l^{-1} . The temporal relationship between changes in plasma quinine and auditory acuity is shown in Figure 1.

Discussion

Quinine has long been known to cause deafness (Morton, 1696), and has also been incriminated as a cause of auditory nerve damage *in-utero*, although the balance of evidence argues against this (Winckel, 1948). In this study the effects of

Figure 1 Changes in mean (s.e. mean) plasma quinine concentrations and mean auditory acuity ($n = 10$) at frequencies from 0.25 to 8 kHz following the initial dose of quinine. Hearing loss denotes the difference between the measured auditory acuity and the mean baseline value before treatment.

antimalarial treatment with quinine on hearing were assessed with a simple portable audiometer in a provincial hospital. We did not test frequencies higher than 8 kHz which may be a more sensitive measure of iatrogenic ototoxicity (Jacobson *et al.*, 1969), and we were unable to exclude ambient noise completely (although this usually interferes only with assessment of low frequency auditory acuity). Nevertheless this study shows that quinine predictably and reversibly induces high tone hearing loss at plasma concentrations in the usual therapeutic range. This was usually unnoticed, did not correlate in magnitude with the complaint of tinnitus or other subjective adverse effects, showed no evidence of tachyphylaxis, but resolved completely when the drug was stopped.

Quinine like many of the ototoxic drugs preferentially affects high tone hearing. In guinea pigs given large doses of quinine, there is degeneration of the organ of Corti which begins with loss of the external hair cells, and may extend to pathological changes in the stria vascularis and internal hair cells (Ruedi *et al.*, 1952). However, such changes are unlikely to account for the rapid onset and offset of hearing changes noted in this study. Vascular alterations, notably vasoconstriction in the stria vascularis, supratrilar ligament and basilar membrane or a direct pharmacological effect on the hair cells may be more relevant (Hawkins, 1976; Koegel, 1985) to rapid reversible changes in hearing. The mechanism of hearing impairment may be simi-

lar to that associated with salicylism. By analogy, quinine also induces rapid and reversible changes in the electroretinogram (Cibis *et al.*, 1973) which are thought to result from a direct effect on retinal cell function.

There is increased plasma protein binding of quinine in malaria (Silamut *et al.*, 1985) principally because of increases in the acute phase protein, α_1 -acid glycoprotein. In this study the mean concentration of free quinine was 6% of the total concentration. Binding is proportional to disease severity and this may explain why serious quinine toxicity is unusual despite plasma quinine concentrations which often exceed 15 mg l⁻¹ in serious disease (White *et al.*, 1982). The number of patients in this preliminary study was too small to determine the precise relationship between total and free plasma concentrations and hearing loss, although auditory acuity declined as quinine levels rose through the therapeutic range, and changed with fluctuations in quinine levels during the course of treatment. High tone hearing loss is usual during the treatment of malaria with quinine, but patients may be reassured that it is reversible.

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