CASE REPORT

The management of quinine-induced blindness

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Quinine is rarely taken in overdose (Pearn *et al.*, 1984; Boland *et al.*, 1985). We present a case where blindness resulted from an accidental overdose of only eight tablets of quinine sulphate. Opinion regarding both the aetiology and the management of quinine-induced blindness has altered in recent years (Boland *et al.*, 1984; Dyson *et al.*, 1985; Dyson *et al.*, 1986). This case suggests that expert advice received regarding this condition may not be that recommended in the light of these changes.

Case report

A 40-year-old man presented to the A&E Department at Hope Hospital at 9 a.m. having become blind overnight. At 8 p.m. the previous day he had developed a mild frontal headache and had taken two of his father's tablets which he believed to be painkillers. His headache did not improve and over the next 8 h he took a further six tablets. During the night he noticed that the street lights became dim and disappeared. When he woke in the morning he was blind and had a buzzing noise in his ears.

On examination both pupils were fixed and dilated and there was no light perception in either eye. Fundoscopy was normal. He appeared to have slight hearing impairment but examination was otherwise normal.

He brought with him the bottle of tablets he had taken. This contained quinine sulphate tablets which had been prescribed for his father for muscle cramps.

Gastric lavage was carried out and repeated doses of activated charcoal were given. The Poisons Information Centre recommended unilateral stellate ganglion block (SGB) after being seen by an ophthalmologist. On the advice of the duty ophthalmologist bilateral SGBs were performed at 5.30 p.m.

The patient regained light perception in both eyes at 11 p.m. on the day of admission and his visual acuity gradually improved. Eight days after admission

his visual acuity was 2/24 in the right eye and 2/6 on the left with marked visual field restriction. On review 2 months later his visual acuity had improved to 6/12 in each eye but his visual fields continued to be greatly constricted.

DISCUSSION

Cinchona bark, which contains quinine is known to have been used in Europe since 1633. In overdose the commonest symptoms are tinnitus, nausea, vomiting, hearing impairment, vasodilation and sweating (Elliott, 1918; Dyson *et al.*, 1985). The commonest permanent disability is visual field restriction, which is frequently severe and may require the patient to be placed on the blind register (Elliott 1918; Dyson *et al.*, 1985 Bateman & Dyson, 1986). The vast majority of patients show some improvement with transient blindness lasting for between 1 h and 50 days. Between 8 and 14 h is typical of the length of time between blindness developing and the first perception of light.

Improvement in visual acuity may continue for some weeks, or even in a few cases for several months or years (Elliott, 1918; Braveman *et al.*, 1948; Boland *et al.*, 1985; Dyson *et al.*, 1985). Visual symptoms have been reported in 17% of a series of patients with quinine overdose (Dyson *et al.*, 1985). A total of 75% of these patients were completely blind but symptoms may be restricted to an alteration in colour vision, visual field restriction or blurring of vision. Typically ocular symptoms develop 4–15 h after overdose (Boland *et al.*, 1985; Dyson *et al.*, 1985; Elliott, 1918).

The pupils may become fixed and dilated some time before the onset of blindness (Bard *et al.*, 1964; Robertson *et al.*, 1979) although the mechanism of pupillary dilation is uncertain (Bacon *et al.*, 1988). Fundoscopy is usually normal at the onset of visual symptoms but after blindness has developed there may be marked changes including constriction of retinal arterioles, retinal oedema and a cherry red spot at the macula. Optic atrophy may develop several weeks or months later (Elliott, 1918; Braveman *et al.*, 1948; Stuart, 1963; Bricknell *et al.*, 1967; Kennerley Banks *et al.*, 1972; Murray & Jay, 1983; Dyson *et al.*, 1985; Canning & Hague, 1988).

The exact mechanism of visual loss has been debated since the 1880's (Elliott, 1918; King, 1934) and is still uncertain. It was initially felt that blindness occurred due to retinal ischaemia secondary to retinal arteriolar constriction (Pelner & Saskin, 1942; Braveman *et al.*, 1948; Stuart, 1963). However blindness has been observed in patients whose retinal arteriolar calibre remained normal (Boland *et al.*, 1985; Thomas, 1984) and others with normal retinal arteriolar calibre when blindness occurred, who, several days or weeks later after sight had returned, developed arteriolar constriction (Elliott, 1918; Braveman *et al.*, 1948; Brinton *et al.*, 1980; Murray & Jay, 1983; Boland *et al.*, 1985; Dyson *et al.*, 1985, 1986; Bacon *et al.*, 1988; Canning & Hague, 1988). This suggests that blindness is not due to retinal arteriolar constriction. Support for the hypothesis that blindness results from a direct toxic effect of quinine on the retina comes from electroretinographic (ERG) studies following quinine overdose. In animal studies ERG changes occur within minutes of the intravenous injection of an LD50 of quinine (Cibis *et al.*, 1964). Histopatho-

logical studies in animals show changes in the photoreceptor cell and ganglion cell layers of the retina (Cassini, 1949; Caffi & Rapizzi, 1966). Doses used in these animal studies were larger than those commonly seen in human poisoning but similar ERG changes have been observed following quinine overdose in man. In humans the ERG changes vary with time, but it appears that the photoreceptor cell layer is affected first followed by the ganglion cell layer, and probably the pigment epithelium (Brinton *et al.*, 1980). There is also evidence of optic nerve damage with increased latency in the visual evoked response from 3 days to about 6 months after quinine overdose (Bacon *et al.*, 1988; Brinton *et al.*, 1980; Gangitano & Keltner, 1980). This may precede retinal arteriolar constriction.

Measures to dilate retinal arterioles have been used in the treatment of blindness due to quinine overdose for 45 years (Redslob *et al.*, 1946; Glick & Mumford, 1955). The commonest method used has been SGB. The vascular effects of SGB occur within minutes of the procedure (Bricknell *et al.*, 1967), whereas in cases where visual improvement was attributed to SGB it usually started some hours after the block was performed (Murray & Jay, 1983; Thomas, 1984; Dyson *et al.*, 1985; Bacon *et al.*, 1988). This suggests that the observed recovery was due to spontaneous improvement. This is the natural history of the majority of cases of quinine induced blindness (Elliot 1918; Boland *et al.*, 1985; Dyson *et al.*, 1985, 1986).

Evaluation of the value of SGB in quinine induced blindness is not straightforward as there have been no prospective controlled trials comparing patients treated with and without SGB. Two series of patients treated with and without SGB have been published (Boland *et al.*, 1985; Dyson *et al.*, 1986) and are summarized in Table 1. As these were retrospective, not randomized and involved small numbers interpretation of the results is difficult but there is no clear evidence of benefit. Many of the papers supporting the use of SGB have been single case reports (Redslob *et al.*, 1946; Glick & Mumford, 1955; Stuart, 1963; Bricknell *et al.*, 1967; Kennerley Bankes *et al.*, 1972; Glick & Mumford, 1955; Redslob *et al.*, 1946; Robertson & Kothanda Raman, 1979; Thomas, 1984) which could be subject to bias. A convincing argument against SGB being of any value is that, in patients who have had unilateral SGB performed, there has been no difference in outcome between the treated and untreated eyes (Dyson *et al.*, 1986; Bacon *et al.*, 1988). The

Table 1. Patients treated with and without SGB.

	All cases	SGB	No SGB
(Boland <i>et al.</i> , 1985)			
Total	39	25	14
Full recovery	17	11 (44%)	6 (43%)
Impaired vision	19	11 (44%)	8 (57%)
Died	3	3 (12%)	0 (0%)
(Dyson <i>et al.</i> , 1986)			
Total	25	20	5
Full recovery	9	8 (40%)	1 (20%)
Impaired vision	16	12 (60%)	4 (80%)

rationale for performing unilateral as opposed to bilateral SGBs is to prevent systemic toxicity of the local anaesthetic agent and other potentially fatal complications including bilateral tension pneumothoraces and recurrent laryngeal nerve palsies (Dyson *et al.*, 1985). For these reasons it was recommended that when bilateral blocks were performed they should be separated by 1–2 h (Robertson & Kothandra Raman, 1979). SGB is not a risk free procedure. Other serious complications include death, apnoea (Adriani *et al.*, 1952), aphasia, hemiparesis (Scott *et al.*, 1983), fits (Adriani *et al.*, 1952; Korevaar *et al.*, 1979) and transient bilateral blindness (Szeinfeld *et al.*, 1981). Therefore, in the absence of any definite evidence of benefit from the procedure its continued use following quinine overdose should be questioned. Other methods have been used to achieve retinal arteriolar vasodilation including intravenous (Perner & Saskin, 1942), inhaled (Elliott, 1918; Braveman *et al.*, 1948; Stuart, 1963; Robertson & Kothandra Raman, 1979; Bateman & Dyson, 1986), and retrobulbar (Bricknell *et al.*, 1967; Robertson & Kothandra Raman, 1979; Dyson *et al.*, 1986) vasodilators, CO₂ inhalation (Bateman & Dyson, 1986) and reducing intraocular pressure by anterior chamber paracentesis (Dyson *et al.*, 1986). These methods have never been studied in a controlled trial but case reports do not show any clear evidence of benefit. This is further support for the idea that blindness following quinine overdose is not due to vasoconstriction. Ocular massage, recumbent posture (Elliott, 1918) and hyperbaric oxygen (Lanski *et al.*, 1983) have also been reported as beneficial in single case reports but again no controlled trials have been performed.

Recommendation for the management of quinine induced blindness

In the absence of any therapeutic manoeuvre of proven benefit in established blindness resulting from quinine its prevention is of paramount importance. Quinine is widely used for the treatment of muscle cramps and is believed by many who take it to be non-toxic. Labelling tablet containers to warn that toxicity may occur from even a small number of tablets taken in excess of the recommended dose might prevent death and permanent disability. Preventing elevated plasma levels may be achieved either by reducing absorption from the gastrointestinal tract or by increasing clearance of the drug from the circulation.

Frequently following an overdose, patients present after the absorption phase of the drug is over. However, *in vitro* quinine is effectively absorbed by activated charcoal (Hayden & Comstock, 1975). Theoretically, if given while quinine is still present in the gut, activated charcoal will bind to it and reduce its absorption.

Of more clinical benefit is the ability of repeated activated charcoal, given orally after the absorption phase is complete, to increase the rate of elimination of quinine from plasma. This has been demonstrated both in volunteers following a therapeutic dose of quinine bisulphate (Lockey & Bateman, 1989) and in patients following overdose where the mean half-life was 8.1 h compared with 24 h in a similar group of poisoned patients not given activated charcoal (Bateman *et al.*, 1985b; Prescott *et al.*, 1989). In one patient despite a 36-h delay between overdose and starting oral activated charcoal the half-life was reduced from 33 h to 10 h (Prescott *et al.*, 1985). There is no evidence that quinine undergoes enterohepatic circulation and it is likely that activated charcoal promotes diffusion down a

concentration gradient from plasma to the gut lumen. The dosage regime used in quinine overdose is 50 g initially, repeated every 4 h to a total dose of 200–400 g.

The majority of the clearance of quinine occurs through hepatic metabolism and because of this forced acid diuresis does not significantly increase the rate of quinine elimination (Bateman *et al.*, 1985a). Peritoneal dialysis, haemodialysis, exchange transfusion and charcoal and resin haemoperfusion only remove a very small quantity of quinine and have not been proven to be of any therapeutic benefit (Burrows *et al.*, 1972; Floyd *et al.*, 1974; Sabto *et al.*, 1981; Morgan *et al.*, 1983; Bateman *et al.*, 1985b). This is presumed to be due to quinine being strongly bound to plasma proteins and having a large volume of distribution (Morgan *et al.*, 1983; Bateman *et al.*, 1985b).

SUMMARY

Given the potential toxicity of even a small number of quinine tablets we suggest that patients to whom these are prescribed should be alerted to this risk both by the prescribing clinician and by a warning, clearly printed on the tablet container. There is no evidence that increased retinal arteriolar dilation is of any value in the management of patients with quinine induced blindness. Therefore the use of SGB for this condition must be questioned unless a controlled trial is performed which shows benefits. We recommend that the aim of treatment has to be reduction in the plasma level of quinine. The most efficient way of accomplishing this is by repeated oral activated charcoal.

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