Blindness from quinine toxicity

P BACON,¹ D J SPALTON, AND S E SMITH²

From the ¹Medical Eye Unit and ²Department of Clinical Pharmacology, St Thomas's Hospital, London SE1

SUMMARY We report a case of quinine overdose in a 47-year-old man who presented with blindness. Fundus photography demonstrates the acute and subsequent retinal changes, and his visual recovery to normal acuity with visual field constriction is documented. Pupillary and electrodiagnostic findings are recorded. Stellate ganglion block has been widely advocated as a helpful therapeutic measure, but our patient was treated with a unilateral stellate ganglion block without apparent benefit to that eye. From a review of the literature we believe that quinine produces its effects by toxicity on the retina rather than by vasoconstriction and that stellate ganglion block probably does not alter the natural history of the retinal toxicity.

Quinine, a naturally occurring alkaloid traditionally used for the treatment of malaria, is now most commonly used in this country for the relief of nocturnal muscle cramps. Acute poisoning induces a syndrome known as cinchonism and is usually seen after attempted abortion, suicide, or accidental poisoning in children.

Visual loss is one of the most common and important effects which has been well reported in the literature, but the site within the retina of the toxic effect and its management have been the subject of discussion and controversy since the turn of the century. We report a case of acute quinine poisoning as a suicidal attempt in a 47-year-old man and document the retinal changes, the pupillary findings, and the electrodiagnostic tests. There have been many reports over the last 20–30 years of the benefits of stellate ganglion block for the treatment of the ocular toxicity.^{1–6} Our patient was treated with a unilateral stellate ganglion block, and we discuss whether or not this treatment can be expected to have any beneficial effect.

Case report

On 9 April 1984 at midday a 47-year-old white male attended the General Casualty Department of St Thomas's Hospital having swallowed 50 quinine sulphate tablets (200 mg, total 10 g) and 20 flurazepam tablets (30 mg, total 600 mg) with an unspecified quantity of alcohol during the afternoon

of the previous day. This was a genuine suicide attempt, but he had vomited prior to sleeping. He complained only of blindness.

When first seen he was generally well, though drowsy, his resting pulse rate being 60/minute, blood pressure 105/60 mmHg, and his electrocardiogram (ECG) showed sinus rhythm with normal electrical patterns. Routine blood tests, including full blood count, electrolyte tests, and liver function tests, were normal. Blood taken 18 to 24 hours after ingestion was sent to the Poisons Unit at Guy's Hospital for drug estimations. Quinine levels were 6.6 mg/l and desalkyl flurazepam 1.1 mg/l.

On admission an eye examination showed visual acuity to be limited to light perception in each eye, the pupils being equal, dilated, and fixed. The results of anterior segment examination and the intraocular pressures were normal. A fundal examination revealed bilateral generalised retinal oedema with bilateral macular cherry red spots, though the retinal vessels appeared normal.

Three hours later a right stellate ganglion block with 10 ml of 0.5% bupivacaine plus 1:100 000 adrenaline was performed. There was no resultant subjective improvement, but a small right ptosis and right miosis were noted.

Subjective assessment of his visual recovery was hindered by functional overlay. On day 2 he claimed to see shadows only, but with a +0.5 dioptre correction he was persuaded to read nearly 6/5 with each eye. He was unable to see the reading text type book. There was minimal pupil reaction to light in the left eye and none on the right. Colour vision testing

Correspondence to D J Spalton, FRCS, Medical Eye Unit, St Thomas's Hospital, London SE1 7EH.

Fig. 1 Optic disc and macula of the left eye taken two days after presentation (11 April 1984). Retinal vessels have normal calibre, retinal oedema is present.

Fig. 2 9 May 1984: the left eye shows optic disc pallor and arterial attenuation with gliotic sheathing of the arteries and veins adjacent to the disc. Retinal oedema has resolved.

with Ishihara colour plates showed 1/17 and 2/17 correct in the right and left eyes respectively; in neither case was the control plate correctly identified. He was unwilling to use a Goldmann perimeter. Fundal examination showed less retinal oedema and normal vasculature (Fig. 1).

On day 4 his vision was 6/5, N8 or better in each eye. He correctly identified three out of six Ishihara plates with each eye, fuller examination being refused. Fundal examination was unchanged. Goldmann visual field testing showed grossly constricted fields, though there was a hysterical stellate pattern in each eye.

At one week there was no further change. At three

weeks (2 May 1984) he returned to the Outpatient Clinic very much more confident and self-assured, complaining of such poor night vision that he had to go to bed by 6 pm every day. The pupils measured 5.5 mm and 5 mm with minimal reactions to light and accommodation. The vision in both eyes was 6/6 and colour vision 5/17 and 8/17, with correctly identified Ishihara plates in the right and left eyes respectively. Fundal examination revealed attenuated arterioles and early disc pallor (Fig. 2). The maculae were normal. Visual field estimation showed gross constriction in both eyes, the right more severe than the left on this occasion (Figs. 3A, B). At six weeks (1 June 1984) his reading and peripheral vision had

Fig. 3A

Fig. 3B

Figs. 3A, B Goldmann fields three weeks after presentation show gross constriction.

Fig. 4A

Fig. 4B

Figs. 4A, B Eight months later visual fields show marginal improvement.

improved a little further and he had normal acuity with full colour vision on Ishihara colour plate testing. The pupils measured 4.5 mm and 3.5 mm. There was minor visual field improvement in both eyes, but the fundi were unchanged.

At six months bilateral peripapillary arteriolar sheathing was noted extending along the vessels for 1–2 disc diameters. Clinical findings were otherwise unchanged except that there was possibly some marginal improvement in visual fields (Figs. 4A, B).

ELECTROPHYSIOLOGY

Recordings of the electro-oculogram (EOG), electroretinogram (ERG), and visually evoked response (VER) were initially performed at 4 weeks. The EOG ratio was grossly reduced at 130% each eye (normal >250%). The dark adapted ERG from the left eye was subnormal with absence of the b wave, the a wave being 300 μ V (normal 150–200 μ V), suggesting a proportionately greater loss of post-synaptic electrical activity than photoreceptor activity. Cone mediated responses were grossly reduced with fusion to a flickering red light at 5 Hz (normal >30 Hz). VERs to high contrast patterns were reduced in amplitude at 1–4 μ V (normal >7.5 μ V), broad, and the P100 wave was delayed at 125–145 ms (normal <115 ms). Responses to low contrast small patterns were abolished.

At 10 weeks the EOG ratio was unchanged at 130%, the ERG showed some evidence of improvement with the appearance of a small b wave (25 μ V, normal range 500–600 μ V). At 5 Hz red flicker ERGs were present at 25 μ V amplitude. The VER amplitude remained unchanged but the response was slightly faster. No further electrodiagnostic studies were done.

In summary, these tests showed electrophysiological evidence of damage in all retinal layers as well as the optic nerve but possibly affecting the bipolar and Müller cells more severely. Two and a half months after the overdose only marginal recovery was found.

PUPILLOGRAPHY

The patient's pupils were studied on three occasions, at 5, 28, and 30 weeks after quinine exposure, by infrared TV pupillography. On both sides the pupils were of normal appearance and diameter in the dark. There were bilateral defects to peripheral light perception, more severe on the right side, in keeping with the loss of peripheral vision. Light reflex responses to flash illumination were greatly reduced on both sides even when the light intensity was appropriately adjusted for the perception defect. The pupillary response to accommodation was reduced, and there was only a small sympathetic dilatation to loud noise.

At the second examination both pupils showed a small response to 2% phenylephrine eyedrops. At the third examination the mydriatic responses to tropicamide 0.5% alone and subsequently to tropicamide plus phenylephrine 10% were within normal limits.

These findings are suggestive of more than one site of involvement in the pupillary pathways. The reduced perception of light is consistent with an afferent defect of retinal or optic nerve origin, but the poor reflex responses also indicate an efferent defect, the site of which is uncertain. It could be neurological or originate in the iris muscle, but the normal response to the anticholinergic drug tropicamide makes a local iris muscle defect less likely. Alcoholic neuropathy might be an additional factor.

Discussion

Quinine is rapidly absorbed from the gastrointestinal tract, producing the typical symptoms of cinchonism, which are tinnitus, headache, nausea, tremor, hypotension, and gastrointestinal upset. There is marked individual variability of tolerance to quinine, but symptoms are likely in any single dose greater than 4 g and death has occurred with as little as 8 g.^{7,8} Quinine is rapidly metabolised and excreted by the kidneys, but clearance may be impaired at toxic levels. Forced acid diuresis and a variety of other methods (exchange transfusion, dialysis, activated charcoal, etc.) have been used to promote excretion of the drug, but these special techniques are probably rarely indicated, and treatment should be aimed at preventing permanent visual damage and life support.

Our patient had the typical ocular changes of acute quinine poisoning. Although he had taken a combination of quinine and flurazepam, no visual toxicity has been associated with the latter. He was seen 18–24 hours after the initial overdose with a moderately large amount of the drug, though the effects of the overdose might have been ameliorated by vomiting. Nevertheless blood levels were moderately high (6.6 mg/l) at this stage. His pupils were fixed and dilated, acuity was limited to perception of light, and funduscopy showed inner retinal oedema with normal retinal vessel calibre (Fig. 1). The visual acuity and field defects rapidly improved (Fig. 3) and his pupils reduced to normal size over about three weeks. Retinal arterial constriction and optic disc pallor were observed to begin about three weeks later with visual field improvement (Fig. 2).

Pupillary dilatation is a consistent feature of acute quinine poisoning, both in humans and experimental animals. It must indicate either a neurological efferent pathway defect or local sphincter paralysis. In some patients the pupillary changes may be so extreme that the patient is left with dilated atrophic pupils.⁹ The precise site of this lesion is obscure, but the response of an induced Horner's syndrome to stellate ganglion block in our and other patients must indicate that the sphincter still retains some contractile power. Formal pupillometry on our patient was not carried out until the acute stages were passed and may also have been complicated by the possibility of an alcoholic autonomic neuropathy. Apart from confirming the presence of both afferent and efferent pupillary defects, we were unable to elucidate the nature of the efferent defect any further at this time. Gangitano and Keltner¹⁰ reported on a patient with quinine toxicity who developed tonic pupillary responses seven months after ingestion. It is not completely clear whether the development of Adie's-

like pupils in this report was directly related to quinine toxicity or could have been coincidental. While our patient was not tested for supersensitivity to pilocarpine, the pupillary reflexes were not tonic at 1 or 7 months, which effectively excludes an Adie's-like pupil.

The electrophysiology on our patient was performed four weeks after the overdose, and the findings of a reduced EOG, loss of the b wave in the ERG, and reduced flicker fusion are in general agreement with the experience of others when these patients were examined in the chronic stage of their illness.^{11,12} The initial changes in the electrophysiology are controversial and there is a voluminous continental literature on the electrophysiological changes found with quinine toxicity.¹³ Some authors have found normal ERGs in the acute phase, but a careful study of an acute case showed that in the earliest stages there was increased a wave amplitude and decreased b wave with a low EOG.¹¹ Within three days the ERG approached normal values, but by the ninth day the b wave had started to decrease and six months later remained essentially unchanged. These findings were corroborated in rabbit experiments,¹⁴ and the authors^{11,14} suggest that these results imply a direct early toxic effect of quinine on the neuroretina.

Successful treatment of the visual loss from quinine depends on a knowledge of the mechanism of toxicity and its localisation in the retina. Accurate information on both these aspects is lacking as little experimental work has been done in recent years. The possibilities are that the retinal changes are due to either arterial vasoconstriction and inner retinal ischaemia or to a direct toxicity of the neuroretina, and these alternatives have been debated since the 1890s without conclusive evidence being obtained for either hypothesis. The fundal appearances simulate a central retinal artery occlusion, but a review of previous reports is confusing on whether the retinal arteries are constricted in the earliest phases. Our patient had inner retinal oedema with normal retinal vessels (Fig. 1) 18–24 hours after overdose, though it is conceivable, but unlikely, that the retinal vessels may have been constricted and dilated again before presentation. Optic disc pallor and retinal vascular attenuation were noted by three weeks after the overdose. The natural history of the toxicity, however, with return of good visual acuity, peripheral constriction of the field, arterial attenuation, and optic atrophy is quite different from that occasionally seen with visual recovery following central retinal arterial occlusion, and this therefore supports the neural toxicity theory. Retinal toxicity also tends to be supported by the electrophysiological evidence already mentioned. There are no adequate reports of the pathology of quinine poisoning in man, though two

Table 1 Effect of stellate ganglion blockade on recovery from blindness caused by quinine toxicity

Reference	Quinine dosage	Initial ocular examination	Time of stellate block	Visual recovery
2	15 g (0.5 oz)	Blind, fixed pupils, pale discs, retinal oedema, narrowing of peripheral arteries	40 hours	6/9 Constricted fields
3	12 g	Blind, fixed pupils, no arterial construction	14 hours +	6/9 6/9 Constricted fields
4	8 g	Blind, fixed pupils, normal arteries, retinal oedema	3 days	6/9 6/9 Fields not known
5	4.5 g	PL, dilated pupils, minimal light reflex, normal fundi	24 hours	6/9 6/9 Constricted fields
6	Not known	Blind, fixed pupils, normal fundi	28 hours	6/12 Fields: too young to assess
22	7.5 g	Blind, arterial narrowing	26 hours	Acuity 'improved', constricted fields (no ophthalmological assessment)
23	19 mg/l plasma	Blind	8 hours	6/6 6/6 Constricted fields

PL=perception of light.

cases have been reported.^{15 16} A review of the early experimental work in various animals shows consistent damage to the ganglion cell and nerve fibre layers and inconclusive vascular changes.¹⁷⁻¹⁹

The pharmacology of quinine is not well known, but there is a suggestion that the drug interferes with the metabolism of acetylcholine.²⁰ There is good evidence to suggest that acetylcholine is a synaptic transmitter in the amacrine cells, and interference with cellular metabolism in this area could lead to cloudy inner retinal oedema. Furthermore, an anti-cholinergic action might explain the mydriasis seen in the acute stage.

In recent years the prevention of blindness from quinine toxicity has focused on the use of stellate ganglion block. Vermes tried this in dogs as a method to produce ocular vasodilatation,²¹ and Redslob *et al.* appear to have been the first to use it in humans.¹ Since then there have been numerous enthusiastic reports of its efficacy, which are surprising in view of the lack of a sympathetic innervation of the retinal vessels or evidence to suggest that quinine toxicity produces spasm of the ophthalmic artery or other arteries elsewhere. In our patient a unilateral sympathetic blockade did not offer any therapeutic advantage to that eye. Although permanent blindness may result from quinine toxicity, there is a natural tendency to improvement, and critical review of many reported cases does not give support for any consistent therapeutic effect (Table 1). Although patients were left with good central visual acuity and constricted fields, there does not appear to be any consistent relationship between the amount of drug ingested and the time of stellate ganglion block and visual recovery. Similar visual recovery has been reported in cases without stellate block.^{9 11 12 24-26} This procedure is not without hazard, potential complications being intra-arterial injection, pneumothorax, or paralysis of the diaphragm or vocal cords by

pharyngeal or recurrent laryngeal nerve palsy. Stellate ganglion blockade therefore appears unlikely to be justified in the management of visual loss from quinine toxicity, which agrees with the experience of Dyson *et al.*,²⁷ who reviewed 48 patients with quinine poisoning, six of whom had visual problems. They found that those patients with the highest blood levels (related to time of ingestion) were most likely to have ocular change. Stellate ganglion block appeared to be ineffective.

We thank Miss Sarah Tindall and Miss Linda Stannard for word processing, and the help of the Iris Fund for Prevention of Blindness.

References

- Redslob E, Warter J, Isch F. Intoxication par la quinine. Traitement de la surdit et de l'amaurose consecutives par des infiltrations stellaires. *Ann Oculist (Paris)* 1946; **179**: 218-20.
- Glick L, Mumford J. Quinine amblyopia treatment by stellate ganglion block. *Br Med J* 1955; **ii**: 94-6.
- Mehenachan J. Quinine amblyopia treated by stellate ganglion block. *Br J Ophthalmol* 1993; **47**: 62-3.
- Bricknell PP, Middleton HG, Hollingworth A, Evans EML. Stellate ganglion block in treatment of total blindness due to quinine. *Br Med J* 1967; **iv**: 400-1.
- Banks JKL, Hayward JA, Jones MBS. Quinine amblyopia treated with stellate ganglion block. *Br Med J* 1972; **iv**: 85-6.
- Valman HB, White DC. Stellate block for quinine blindness in a child. *Br Med J* 1977; **i**: 1065.
- Polson CJ, Tattersall RN. *Clinical toxicology*. London: English Universities Press, 1959.
- Black ECG, editor. *Isolation and identification of drugs*. London: Pharmaceutical Press, 1969; **1**: 533.
- Knox DL, Palmer CAL, English F. Iris atrophy after quinine amblyopia. *Arch Ophthalmol* 1966; **76**: 359-62.
- Gangitano JL, Keltner JL. Abnormalities of the pupil and visual evoked potential in quinine amblyopia. *Am J Ophthalmol* 1980; **89**: 425-30.
- Zahn JR, Brinton GF, Norton E. Ocular quinine toxicity followed by electroretinogram, electro-oculogram and pattern visually evoked potentials. *Am J Optom Physiol Opt* 1981; **58**: 492-8.
- Franois J, de Rouck A, Cambie E. Retinal and optic evaluation in quinine poisoning. *Ann Ophthalmol* 1972; **4**: 177-85.

- 13 Hommer K. Über die Chininvergiftung der Netzhaut. *Klin Monatsbl Augenheilkd* 1968; **52**: 785–805.
- 14 Cibis GW, Burian HM, Blodi FC. Electroretinogram changes in acute quinine poisoning. *Arch Ophthalmol* 1973; **90**: 307–9.
- 15 Fortunati A. Ricerche istologiche sopra un caso di cecità da chinina nell'uomo. *Riv Ital Ophthalmol* 1905; **1**: 5–16.
- 16 Giannini D. Dell'influenza dei disturbi di circolo sulla patogenesi delle alterazioni funzionali ed anatomiche del nervo ottico e della retina negli avvelenamenti da chinino. *Ann Ottalmol Clin Oculist* 1934; **62**: 1069–88.
- 17 Holden WA. The pathology of experimental quinine blindness. *Trans Am Ophthalmol Soc* 1897–9; **8**: 405–11.
- 18 Forster AE. An experimental study of the pathogenesis of quinine amblyopia with special reference to ethylhydrocuprein hydrochloride. *Am J Ophthalmol* 1923; **6**: 376–80.
- 19 de Schweinitz GE. Additional experiments to determine the lesion in quinine blindness. *Trans Am Ophthalmol Soc* 1891–3; **6**: 23–9.
- 20 Goodman LS, Gilman A. *The pharmacological basis of therapeutics*. 7th ed. New York: Macmillan, 1985: 1041–4.
- 21 Vermees L. Experimentelle chinin amaurose. *Z Augenheilkd* 1905; **14**: 337–9.
- 22 Robertson DH, Raman KR. Quinine poisoning. *Anaesthesia* 1979; **34**: 1041–2.
- 23 Thomas D. Forced acid diuresis and stellate ganglion block in the treatment of quinine poisoning. *Anaesthesia* 1984; **39**: 257–60.
- 24 Drance SM. Quinine amaurosis. *Br J Ophthalmol* 1955; **39**: 178–81.
- 25 Bard LA, Gills JP. Quinine amblyopia. *Arch Ophthalmol* 1964; **72**: 328–31.
- 26 Brinton GS, Norton EWD, Zahn JR, Knighton RW. Ocular quinine toxicity. *Am J Ophthalmol* 1980; **90**: 403–10.
- 27 Dyson EH, Proudfoot AT, Prescott LF, Heyworth R. Death and blindness due to overdose of quinine. *Br Med J* 1985; **291**: 31–3.

Accepted for publication 27 January 1987.