Ocular quinine toxicity

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SUMMARY A case of ocular quinine toxicity is described which showed the typical acute visual loss and subsequent recovery. Vermiform motion of the pupil was noted 48 hours after overdose. This acute effect has not been reported before. Although acute systemic intoxication may respond to removal of quinine from the gut and circulation, there is no evidence that any treatment affects the visual prognosis. The action of quinine on the retina is unknown. We suggest it may block cholinergic neurotransmission in the inner synaptic layer.

Quinine is one of the few drugs which has altered the course of history. The activity it has against malaria allowed the habitation of large parts of the globe. Quinine toxicity is still a problem today,^{1,2} but little progress has been made in defining the mechanism of its retinal toxicity. We present a case of quinine overdose and speculate on a possible way in which it may affect the retina.

Case history

A 28-year-old woman presented one morning 12 hours after ingesting 9 g of quinine sulphate in an attempt to commit suicide. Within two hours of taking the tablets she had vomited. She noticed tinnitus, fluctuating deafness, rapid palpitations, and paraesthesia on her face. She did not become aware of visual symptoms until the morning, when she awoke totally blind. She was otherwise in good health. The quinine had been prescribed for foot cramps of unknown cause. She had had no previous eye disease.

She was transferred to Moorfields Eye Hospital that day. Twenty-four hours after the overdose the corrected vision was 6/18 right and 6/12 left. Both pupils had a diameter of 9 mm in ambient light and reacted slowly to light and accommodation. There was no relative afferent pupil defect. The intraocular pressures were normal. There was retinal oedema at the posterior poles, and the retinal vessels were engorged.

The serum quinine level was measured on three occasions. Sixteen hours after the overdose it was

8.2 mg/l, at 20 hours it was 6.4 mg/l, and at 48 it was 3.1 mg/l. A forced acid diuresis had been started at the referring hospital. This was discontinued and no other treatment was given.

Her visual fields on the first day in hospital were markedly constricted. They improved progressively over two months until they were almost normal. The Farnsworth Munsell 100-hue test (Fig. 1) remained grossly abnormal over two months. No specific pattern of dyschromatopsia was identified. The central acuity improved over the two months to 6/9

Fig. 1 The Farnsworth Munsell 100 hue test was done under the same lighting level and with the same test set on each occasion. The time scale refers to the number of days elapsed from taking the overdose.

Fig. 2 Retinal vessel calibres: the y axis scale is the diameter in μm of the vessels measured on retinal photographs. Five points were selected on veins and five on arteries in each eye which could reliably be identified on serial photographs. The bars are the cumulative diameters at these five points. The x axis time is the number of days elapsed from taking the overdose.

right and left, and the retinal oedema resolved. The retinal vessels became attenuated, and optic disc pallor developed.

Retinal vessel calibres were measured by an image analysis method developed at the Royal College of Surgeons of England (Fig. 2). Red-free fundus photographs were taken in mid-diastole with a Canon wide-angle fundus camera. The blood pressure and intraocular pressure were recorded. Vessel calibres were measured on the photographs at several sites chosen where they could be identified on serial photographs.

Vermiform pupil motion was noted in both eyes on the day after the overdose. It persisted for the duration of follow-up. Instilling 0.125% pilocarpine drops into one eye produced a brisk miosis.

Electrophysiological studies were done on day 1 and repeated several times, the last being day 66. The electroretinogram (ERG) done on day 1 showed a

normal amplitude to blue, red, and white stimuli, though the oscillatory potentials were reduced. The response to flicker was delayed and abnormal. The pattern ERG was markedly reduced, and no pattern visual evoked response (VER) could be recorded. A flash VER did show a small response with a normal latency. The visual acuity at that time was 6/18 right and 6/24 left, with a markedly constricted visual field and normal retinal vessel calibres.

Subsequently, the ERG amplitude became reduced (Fig. 3). The abnormal flicker response and pattern ERG persisted. A pattern VER was recordable for high contrast gratings, but with an increased latency. A dark adaptation test was attempted on one occasion but could not be interpreted owing to large variations in the response.

Discussion

This case is quite typical of quinine overdose. Early in the course, when the visual acuity was poor, the retinal vessel calibre looked normal. As the vision improved the vessels became attenuated and disc pallor developed. Smith, in 1919, called this the 'paradox of quinine'.³ The role of vessel calibre changes in the pathogenesis of visual impairment is still uncertain.^{1 2 4-12}

TREATMENT OF RETINAL QUININE TOXICITY

This patient received no treatment apart from a brief forced acid diuresis. The wide range of remedies that have been tried in this condition, ranging from strong coffee¹³ to haemoperfusion,¹⁴ reflect both the physician's desire to do something in the face of the usually dramatic loss of vision and the current lack of understanding of the pathogenesis of this form of

Fig. 3 Electrophoretogram: the flash ERG to blue light under scotopic conditions done on day 1 and day 66.

blindness. Treatments are aimed either at reducing the serum quinine level or at preventing or reversing retinal vessel spasm.

The serum quinine level can be reduced by inhibiting quinine absorption from the gut, and perhaps by measures to remove it from the circulation or promote its excretion in the urine. Activated charcoal, if given early, can reduce absorption from the gut. Quinine otherwise is rapidly absorbed, and the serum level reaches a peak in one to three hours.¹⁰ Most quinine is excreted in the urine.¹⁴ It has long been held that urinary excretion can be facilitated by forced acid diuresis, that haemodialysis can produce a rapid drop in serum level, and that plasmapheresis can remove the protein-bound fraction of the serum quinine (about 70%). Recent work has challenged all these assumptions,¹⁵ however, and the subject is controversial.

The methods advocated for dilating the retinal vessels include various vasodilators given orally, parenterally, and within the orbit; massage of the globe; paracentesis; carbon dioxide inhalation; recumbent posture; and stellate ganglion blockade.⁷ No paper has yet shown that any of these methods offers a better visual prognosis than not treating the patient at all. Some methods, such as stellate ganglion block, have a considerable morbidity.¹⁶ Therefore, while life threatening systemic toxicity must be treated, treatment aimed purely at the visual loss is more difficult to justify.

VERMIFORM PUPIL MOTION

This patient displayed vermiform motion of the pupils with enhanced sensitivity to 0.125% pilocarpine drops within 48 hours of the overdose. Hippus was reported in several early papers,^{13,17} which may actually have been vermiform motion. A case of tonic pupil with denervation supersensitivity has been reported in a patient 10 months after overdose.¹⁸ This does not appear to have been noted as an early feature of quinine toxicity, however.

The effect may be due to damage to the parasympathetic nerves supplying the iris, to the neuromuscular junction, or to the sphincter pupillae itself. Quinine has a curare-like action,¹⁰ and so perhaps inhibition of acetylcholine release at the neuromuscular junction may promote the 'denervation supersensitivity' suggested by the miosis to 0.125% pilocarpine.

Quinine is also an irritant drug which has been used as a sclerosing agent in the past. It may damage the vessels supplying the iris. This is thought to be responsible for the iris atrophy seen in some cases.¹⁸ Acute ischaemia of either the sphincter muscle or its nerve supply may have produced the abnormal pupil response.

PATHOGENESIS OF RETINAL TOXICITY

The mechanism of the toxic action of quinine is unknown. The dramatic initial visual loss is not due to retinal ischaemia, since the vessel calibres at that time are normal. The drug must therefore affect the retinal neurones directly. Most electrophysiological studies on patients, including our own, have been done more than 12 hours after the overdose, and the ERG at that time may be normal. The ERG then becomes progressively more abnormal for at least three weeks.⁹

Typically the a-wave deepens and the b-wave shrinks. The photopic component is affected more than the scotopic. Oscillatory potentials are absent, and the flicker response is reduced or absent. The severity of the changes broadly correlate with the degree of visual impairment. These findings suggest that the outer retinal elements are less affected than the bipolar cells.⁹ Similar ERG findings have been observed following central retinal artery occlusion.

A normal early ERG in the presence of severe visual dysfunction suggests that quinine must affect an 'electrically silent' part of the retina initially, such as ganglion cells, which do not contribute to the flash ERG waveform. Moreover the abnormal pattern ERG and reduced oscillatory potentials during the same period, such as was noted in our patient, support the view that the inner retina is mostly affected. Often the only visible abnormality in the fundus at this time is nerve fibre layer oedema, and there is some histological evidence showing damage to this layer.⁴

Two observations have challenged the central role of ganglion cell toxicity in acute quinine blindness. Several workers have now found that the ERG within the first 12 hours of the ingestion of quinine may not be normal.^{8,19} In experimental models the ERG changes within minutes of quinine administration—the a-wave deepens and the b-wave reduces, and this reverts to normal within 24 hours.⁸ Similar findings have been reported in a few patients.¹⁹ This may represent a global retinal toxicity from quinine in its role as a 'general protoplasmic poison'.¹⁰ The fact remains that patients are blind with normal flash ERG recordings, however, so more specific inner retinal toxicity must also occur.

The second observation is that the electrocyclogram (EOG) is grossly abnormal, with no light rise, in the acute phase of quinine toxicity.¹⁸⁻²⁰ It reverts to normal later and may parallel the course of the visual impairment. This is interpreted as a loss of function at the photoreceptor/pigment epithelium level.²⁰ Henkes and Deutman²¹ noted that both the EOG and the a-wave of the ERG depend on photoreceptor function, however, and that an as yet unexplained discrepancy exists between the abnormal EOG and

normal flash ERG in acute quinine toxicity. It seems quite likely, therefore, that both the outer and inner retinal layers are affected.¹⁸

Quinine may possibly act as an antagonist of a neurotransmitter. If this is so, acetylcholine is most likely to be affected, for several reasons:

(1) Quinine has a curare-like action on neuromuscular junctions.¹⁰ The action can be competitively antagonised by neostigmine. It also has other anticholinergic actions such as mydriasis and sinus tachycardia.

(2) The inner synaptic layer of the retina, where quinine may be acting, stains heavily for acetylcholinesterase,²² indicating that acetylcholine is present in the layer. It is one of at least five proposed neurotransmitters in the inner synaptic layer, together with gamma amino butyric acid (GABA), glycine, dopamine, and serotonin.²³

(3) Ganglion cells are thought to be cholinergic neurones. Electrophoretically applied acetylcholine excites off-cells and inhibits on-cells. Some workers²³ have suggested that the effects of acetylcholine are mediated via nicotinic receptors and can be blocked by curare. Quinine, with its known curare-like action, may act here.

(4) A subpopulation of amacrine cells also probably synthesises acetylcholine as a neurotransmitter.²³ Iontophoretic application of acetylcholine suggests that these cells stimulate phasic ganglion cells. Quinine again may block this action.

(5) Almeida⁵ notes that Giannini²⁴ found simultaneous administration of quinine and acetylcholine to dogs can prevent the toxic effects of quinine on the retina.

Quinine may produce acute blindness by interfering with cholinergic neurotransmission in the inner synaptic layer. If this is the mechanism of action, it may be possible to modify it pharmacologically. This acute visual loss, however, will usually at least partly recover. The component of visual loss which is permanent most needs treatment. It is even now not possible to say whether this is the result of irreversible acute retinal toxicity or secondary to retinal vascular insufficiency. Future studies will need to address this problem.

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