POSITIVE RESPONSE TO EDROPHONIUM IN DEATH ADDER (*ACANTHOPHIS ANTARCTICUS*) ENVENOMATION

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Abstract:
A 20-year-old Papua New Guinean male developed neuromuscular paralysis following a bite by a death adder (*Acanthophis antarcticus*). Ptosis persisted despite otherwise effective anti-venom therapy. The ptosis clinically resembled myasthenia gravis and improved after intravenous edrophonium. The role of anticholinesterase drugs in snake bite management is discussed. (Aust NZ J Med 1988; 18: 792-794).

Key words: Snake bite, death adder, neurotoxic envenomation, anticholinesterases.

A case of death adder envenomation is described. Persistent neurotoxic signs of envenomation clinically resembled myasthenia gravis, and were improved by anticholinesterase administration.

CASE REPORT

A previously well 20-year-old male was admitted to Madang General Hospital, Madang, Papua New Guinea following a snake bite 12 hours earlier. He had been bitten on the left foot by a short snake which he subsequently killed and identified as a death adder. On admission he had signs of envenomation with almost complete bilateral ptosis, restricted vertical movements of both eyes, inability to swallow saliva, inability to open his mouth or protrude his tongue. In addition, he had generalised mild weakness of all limbs and evidence of intercostal muscle paralysis. There was no clinical evidence of coagulopathy or rhabdomyolysis.

He was given two ampoules (6 000 units per ampoule) of death adder anti-venom (Commonwealth Serum Laboratories) with resolution over two hours of all signs of envenomation except for persistent bilateral partial ptosis. Such ptosis was still present, unchanged, 24 hours later. Furthermore, it exhibited myasthenic features, with fatigue on repetitive upward eye movements. There was no evidence of weakness or fatigue in other muscle groups. Four days after admission, ptosis had resolved fully with myasthenic features no longer evident.

METHODS

To help confirm the identity of the snake, the patient and guardian were shown a collection of different formalin-preserved snakes, kept at Madang Hospital.

Twenty-four hours after admission, the patient was challenged with intravenous edrophonium chloride (tensilon), an anticholinesterase drug used in the diagnosis of myasthenia gravis. The challenge was performed in double blind fashion as described by Watt *et al.*[1] Atropine sulphate (0.6 mg) was given intravenously, followed immediately by edrophonium chloride (10 mg) intravenously. Identical volumes of placebo (normal saline) were given in similar fashion. Syringes were labelled with code numbers by an independent observer. Response was assessed by measurement of: the percentage of iris uncovered during maximal effort to open both eyes; and the number of seconds that upper lid retraction could be maintained during upward gaze. Baseline readings were taken prior to injection of placebo and edrophonium. Responses were recorded, for both placebo and edrophonium, at zero minutes, five minutes and, thereafter, every five minutes for 30 minutes from the completion of the injections. The code for syringe identification was consulted upon completion of the test. Placebo had been given for the first half of the test and edrophonium for the latter.

RESULTS

From the collection of formalin-preserved snakes, the patient and guardian selected a death adder as identical to the snake that had bitten the patient, and which they had subsequently killed.

Rapid improvement in both measures of muscle power was seen following intravenous edrophonium (Fig. 1). Whilst this improvement was short-lived, no such improvement was seen after placeo injection.

DISCUSSION

Interest in the usage of anticholinesterase drugs, in the management of snake bite, has been revived by Watt following a study of patients envenomated by the Philippine cobra (*Naja naja philippinensis*).[1] That study demonstrated significant improvement in neurotoxic signs of envenomation following edrophonium administration.

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Neurotoxic signs that improved included ptosis, dysarthria and dysphagia. Improvement in respiratory function was also demonstrated in one patient. In the patient described above, improvement in ptosis was investigated as other signs of envenomation had resolved with specific anti-venom therapy. Persistent ptosis after otherwise successful anti-venom therapy is not uncommon because the levator palpebrae superioris muscle is most sensitive to the neuromuscular block caused by neurotoxic snake venoms.

The Australian death adder is, for practical purposes, identical to the Papua New Guinea death adder,[2] so that observations in Papua New Guinea are applicable to bites by the Australian death adder. Death adder venom is highly neurotoxic and, clinically, has no significant coagulant or myolytic action.[2] Early studies of the effects of the crude venom in cats and rabbits suggested that it had a curare-like action.[3] A neurotoxin, acanthophin a, has been isolated from death adder venom.[4] Acanthophin a has a molecular weight of 7 700 and is a single polypeptide chain of 63 amino acids, with four cross-linking disulphide bridges. Its physiological action is due to blockade of nicotinic acetylcholine receptors on the post-synaptic membrane of the motor endplate (I. Spence, unpublished paper). The activity of acanthophin a accounts for the symptoms observed in crude envenomation.[4]

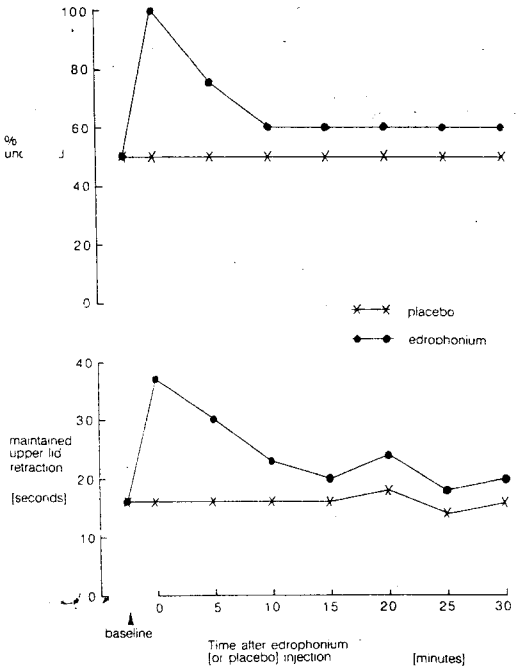

Figure 1: Response of ptosis to intravenous edrophonium chloride (10 mg) compared to intravenous normal saline (placebo). 'Baseline' indicates readings obtained, on maximal effort, before injection of edrophonium and also before placebo.

Snake venom neurotoxins which act by binding presynaptically at the neuromuscular junction often induce ultrastructural changes in the presynaptic membrane. This action prevents neurotransmitter release and causes paralysis. Notexin (in *Notechis scutatus* venom) and taipoxin (in *Oxyuranus scutellatus* venom) are examples of such neurotoxins. These effects do not easily reverse after administration of anti-venom so that, clinically, one sees a paralysis, the progression of which is halted rather than reversed. This contrasts with the often rapid (within 30 minutes) reversal of paralysis seen in death adder bites following the administration of specific anti-venom. Clinical effects of snake venom neurotoxins which act post-synaptically are often indistinguishable from those seen in myasthenia gravis.[5] Electromyographic features may also be identical to those of myasthenia gravis.[6] Much basic research in myasthenia gravis involved the use of α-bungarotoxin, from the venom of the Asian krait (*Bungaris multicinctus*), which binds to nicotinic acetylcholine receptors. α-Bungarotoxin is one of a group of single polypeptide snake venom neurotoxins. The main Australian snake venoms contain at least one of these neurotoxins. They have similar molecular weights (6 000 to 8 000) and they all bind to the acetylcholine receptor causing a curare-like blockade. They differ, however, in the reversibility of their neuromuscular blockade by neostigmine.[7] Lee classified these neurotoxins into two groups according to their amino acid compositions.[8] One group includes those neurotoxins with four disulphide bridges (eg cobrotoxin). These demonstrate reversibility of neuromuscular blockade with neostigmine. The second group includes those neurotoxins with five disulphide bridges (eg α-bungarotoxin) whose neuromuscular blockade is irreversible with neostigmine. On structural criteria acanthophin a would be a member of the former group. Reversibility of blockade with anticholinesterases, as shown in this case study, is also compatible with this classification.

Anticholinesterases have shown some benefit in treatment of snake bite in Asia.[1,9,10] No benefit was demonstrated in Papua New Guinea.[11] In the latter case, no benefit was seen because the snakes involved were probably those whose venoms mainly acted presynaptically, eg Papuan taipan (*Oxyuranus scutellatus canni*). This is often the situation in many cases of snake bite in Australia. It has been stated that there is no place for the use of neostigmine in the management of snake bite in Australia.[12] This statement may not apply to cases of death adder envenomation, as presynaptic neurotoxins appear to be unimportant clinically. The persistent ptosis in this patient clinically resembled myasthenia gravis and showed a positive response to edrophonium. This indicates that anticholinesterase drugs can supplement the action of specific anti-venom in cases of death adder envenomation, especially since the ptosis persisted despite administration of anti-venom and reversal of other signs of envenomation. The death adder is one of the most widely distributed significant venomous land snakes in Papua New Guinea and Australia (except Victoria and Tasmania). Whilst adequate first aid measures, initially, and administration of specific anti-venom (when indicated) are central to the management of snake bite,

anticholinesterase drugs may be useful adjuncts in cases of death adder envenomation. This may be especially so in Papua New Guinea, where anti-venom cost and facilities for its storage are often major concerns. In many provinces in the New Guinea region the death adder is by far the most common cause of serious snake bites. It is in these areas that anticholinesterases may be useful. The most appropriate anticholinesterase agents and their dosages can only be delineated by further study.

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