The use of anticholinesterase therapy

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Introduction

Postsynaptic neurotoxins compete with the acetylcholine (ACh) that is released from nerve terminals at the neuromuscular junction for available nicotinic ACh receptor sites on adjacent skeletal muscle cell synaptic clefts. The binding of these types of toxins to the receptor prevents acetylcholine from depolarising the muscle, producing paralysis. Unlike the extremely destructive paralysis that is caused by phospholipase A_2 presynaptic neurotoxins, postsynaptic snake venom neurotoxins tend to be reversible. This means that once bound by antivenom, these toxins dissociate from the receptor binding site and nerve impulse conduction resumes. This resumption may be either rapid or gradual, depending upon the individual toxins and their respective binding affinities. Rapid early responses to antivenom with varying degrees of persistent residual neurotoxicity have been documented.

Acetylcholine, once discharged from the presynaptic vesicles in the axolemma of the nerve terminal, is rapidly bound by acetylcholinesterase; this breaks down the acetylcholine into its component parts, choline and acetate. These are then taken back up into the nerve terminal and recycled to produce new acetylcholine molecules. This process of release, breakdown and reuptake continues to take place in the presence of postsynaptic neurotoxicity even though there the blockade of the binding site by the toxin prevents acetylcholine from accomplishing its job of depolarising the muscle and initiating contraction or relaxation. The result is that even though postsynaptic paralysis is present, the nerve continues producing neurotransmitter, which only fails to accomplish the task of initiating movement because of excessive competition for binding sites caused by the presence of the toxins.

The reality is that, in each synapse, there are large numbers of receptors for acetylcholine, but the short life of the molecule (before it is split back into acetate and choline by acetylcholinesterase) prevents it from finding unaffected receptors and activating the muscle. This opens a unique window for potential non-antivenom intervention in postsynaptic paralysis induced by snake venom neurotoxins. Anticholinesterases are drugs that inhibit the process of acetylcholine breakdown and reuptake. These drugs allow acetylcholine to remain in the synaptic for considerably longer than they would ordinarily, and this prolonged presence gives acetylcholine greater opportunity to bind to unblocked nicotinic ACh receptor sites on the muscle cell.

The result can be a limited improvement in neuromuscular function and restoration of normal physiological function. Patients who have been treated with anticholinesterases after the bites of death adders (Acanthophis spp.) in Papua New Guinea have experienced improvements that were measurable and functional. Co-administration of anticholinesterase with antivenom to death adder victims has been shown to reduce the time to resolution of neurotoxicity, and even when given without antivenom, anticholinesterases have the potential to improve the neuromuscular function of the envenomed patient.

Clinical evidence of efficacy

Lalloo et al (1996) observed that in patients treated concomitantly with antivenom and the anticholinesterase drug neostigmine (0.45 mg) (with 0.6 mg atropine) that the recovery of neuromuscular effort was significant. One patient who had been intubated experienced recovery of respiratory effort sufficient to enable extubation within 2 hours of administration:

> **CASE REPORT** (from Lalloo *et al*, 1996)
>
> A seven-year-old girl was bitten on the right instep by a 34-cm-long death adder close to a stream where she had been drinking. The snake was killed, and she was taken to a local health centre where a compression bandage was applied. When she arrived at the hospital, 3.5 h after the bite, she was complaining of pain in the right groin and had been vomiting. Symptoms of neurotoxicity, heavy eyelids and difficulty in swallowing, had started about an hour and a half after the bite and she was beginning to have difficulty in breathing. On examination, there was tenderness but no swelling over two fang marks and she had tender lymph nodes in the groin. She had moderate ptosis, a partial ophthalmoplegia, and had developed pooling of secretions because of difficulty in swallowing. Respiratory efforts were weak and involved the diaphragm only. The whole blood clotting time was normal. She was immediately intubated and ventilated by hand. One ampoule of death adder antivenom was infused over 20 min, and she was given 0.45 mg neostigmine and 0.6 mg atropine intravenously. Over the following 2 h, there was a distinct improvement in the level of respiratory effort and the patient was extubated. Mild ptosis persisted, but 14 h after admission to hospital, all signs of neurotoxicity had disappeared and the patient made an uneventful recovery.

In another case reported by Hudson (1988) a 20 year-old man bitten by a death adder (*Acanthophis* spp.) had rapid resolution of most neurotoxicity within 2 hours after antivenom therapy, but had persistent ptosis. Treatment with atropine (0.6 mg) and an anticholinesterase drug, edrophonium (10 mg) resulted in clear improvement.

According to Little *et al* (2000), a patient bitten by a death adder (*Acanthophis antarcticus*) in Australia had significant improvement in lung expansion after treatment with neostigmine (1 mg) and atropine (0.6 mg) that was sustained in duration. Further treatment with 2.5 mg neostigmine and 1.2 mg atropine effectively resolved neurotoxicity altogether. Currie *et al* (1998) treated a Papua New Guinea man who had ptosis, difficulty swallowing and speaking, and respiratory difficulty after a death adder bite with 2.5 mg neostigmine and 1.2 mg atropine. The previous symptoms resolved very rapidly (within 5 minutes).

Limitations of acetylcholinesterase therapy

Anticholinesterase drugs have no value in the treatment of presynaptic neurotoxicity, such as that caused by Papuan taipans (*Oxyuranus scutellatus canni*). There is also no evidence at the present time to suggest that they have clinical value in treating the bites of Papuan blacksnakes (*Pseudechis papuanus*), mulga snakes (*Pseudechis cf. australis*), small-eyed snakes (*Micropechis ikaheka*) or brown snakes (*Pseudonaja cf. textilis*).

Anticholinesterases may suffice to improve muscle power in death adder (Acanthophis spp.) bites, and the effects may only be transient. Obviously, in the context of significant neuromuscular blockade with respiratory failure, these drugs are no substitute for antivenom therapy and mechanical ventilation.

The use of anticholinesterases is only justified in the treatment of known death adder bites, and preferably as an adjunct treatment with antivenom.

Contraindications to use

You should **not use** anticholinesterase drugs if any of the following apply:

- There is a positive 20WBCT (incoagulable blood).
- The patient has spontaneous bleeding and the 20WBCT has not been done.
- The patient describes a snake larger than 1 metre in length.
- The patient describes a snake with a '*red stripe on the back*' or a '*blacksnake with a red back*'.
- The patient describes a '*white snake*', or a '*pale snake with a dark head*'.
- Previous allergy to the drug.

Assessment of suitability

A useful gauge of whether a patient with neurotoxic envenoming might benefit from anticholinesterase therapy is to try the "Tensilon test", using the short-acting anticholinesterase drug edrophonium chloride:

1. Administer atropine sulphate (0.5-1.0 mg for adults, 20 μg/kg for children) IV, then;
2. Edrophonium chloride (10 mg in adults, 0.10 mg/kg in children) by slow IV injection; or, by first giving 20% as a test dose, followed by the remainder 1 minute later;
3. Look for signs of improving muscle power after 10 minutes.

If improvement occurs, then administer and maintain **neostigmine** (much longer-acting):
Dosage: adults 1.25-2.5 mg, children 50-70 μg/kg/dose, by slow IVI, repeated every 2-4 hours whilst weakness remains, if an initial improvement in motor function is observed.

When moderate to large doses of neostigmine, such as this, are given, **atropine** must be given to counteract the unwanted muscarinic side effects of neostigmine, which include bradycardia, increased salivation and sweating:

Dosage: adults 0.6-1.2mg, children 0.02mg/kg, by slow IVI, repeated approximately 6-hourly, depending on the reappearance of excessive salivation or sweating and on the continued use of neostigmine.

Neostigmine is the only anticholinesterase that has been used for snakebite in PNG, although there are other anticholinesterase drugs available. Clearly, if the patient is already intubated and ventilated, this test is only helpful in deciding whether to give death adder monovalent antivenom – in that setting further neostigmine is not required, except on the odd occasion, as above, when there is persistent ptosis, or other neurological deficit, several hours after dose of death adder antivenom.

References

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