ARTICLE

Antivenom update

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SUMMARY

Recent research has found that one vial of antivenom is sufficient for the treatment of envenomation by all five major groups of Australian snakes.

In snake bite coagulopathy, serial coagulation testing helps determine when patients can be safely discharged, but abnormal results are not an indication for further antivenom.

Clinically significant rhabdomyolysis is more common than previously realised in red-bellied black snake envenomation. Early antivenom administration may prevent rhabdomyolysis, but it is unclear if this benefit outweighs the risk of adverse reactions to antivenom.

Analgesia is the mainstay of treatment for redback spider bite.

Early and effective cardiopulmonary resuscitation is more important than antivenom in box jellyfish envenomation.

Introduction

Antivenoms have been used in Australia since tiger snake antivenom was released for general use by the Commonwealth Serum Laboratories in late 1930.[1] By 1962 all the currently used snake antivenoms (taipan, brown, death adder, Papuan black, sea snake and polyvalent) had been developed. Tick, redback spider and stonefish antivenoms were also available. The last two antivenoms released were for box jellyfish (1970) and funnel-web spider (1980).[1] Despite this long history it is only very recently that the clinical specificity, safety and effectiveness of antivenoms have been critically examined.[2]

Pharmacology

Antivenoms are polyclonal antibody preparations produced from the plasma of animals (usually horses or sheep) which have been repeatedly injected with venoms. They can be whole IgG molecules or processed to create antigen-binding fragments. These polyclonal mixtures contain antibodies of varying titre and affinity to the different toxins in the venom. If venom from just one species is used to immunise the animal then the resulting antivenom is termed 'monovalent'. Polyvalent antivenoms are those taken from animals given multiple different venoms or are made from a mixture of monovalent antivenoms.

Clinical effectiveness should not be assumed

Many snake bites, even from venomous snakes, do not lead to envenomation ('dry bites'). It is recommended to give antivenom only when there is evidence of systemic envenomation (for example coagulopathy, weakness). Further, even though all the antivenoms appear to bind with high affinity to venom and neutralise venom-mediated effects under laboratory conditions, the ability of some antivenoms to reverse or prevent all clinical aspects of envenomation has recently been cast in doubt.[2]

Brown snake

As for other antivenoms, the original recommendation for the initial dose of brown snake antivenom was one vial.[3] This contained enough antivenom to neutralise the venom from a milked snake. However, for many years steadily increasing amounts were given to patients with venom-induced consumptive coagulopathy and the recommended initial doses were increased.[4] Recommendations were being made based on the number of doses of antivenom being given before coagulation returned to normal.

Crucially, there was a failure to consider that recovery from coagulopathy requires resynthesis of clotting factors by the liver. This process usually takes around 12–18 hours. Testing clotting function before this time always returns abnormal results and should not be used to guide repeat antivenom dosing.

Recent studies have confirmed that repeated or larger initial doses of antivenom do not hasten

Fig. 1 **Tiger snake**

Courtesy of Scott Eipper

Correction November 2012
Fig. 1 image replaced.

recovery.[5,6] The clinical toxicologists and toxinologists in Australia have therefore returned to the original recommended dose of one vial. Serial coagulation tests should be done to determine when the patient is safe to discharge, not to decide when to give more antivenom.[7]

One vial appears sufficient for most snakes

The Australian Snakebite Project is an ongoing, multicentre, prospective, observational study that recruits patients with suspected snakebite and snake envenomation from over 120 major tertiary and regional hospitals and associated major poisons information centres.[8] Demographic details, clinical effects, laboratory information and treatments are recorded and patients have serial serum samples collected for venom and antivenom quantification. This project has shown that one vial of tiger snake antivenom is sufficient for rough-scaled snake envenomation[8] and one vial of taipan antivenom is sufficient for taipan envenomation.[9] The dose for mulga (king brown) and death adder envenomations has always been one vial.

Red-bellied black snake bite may be undertreated

Red-bellied black snakes were thought to just cause non-specific systemic effects, mild rhabdomyolysis and local effects which could be managed without antivenom.[5] The Australian Snakebite Project found that 95% of patients developed systemic symptoms and there was a previously unrecognised, but clinically significant, myotoxicity. This resulted in longer hospital stays and admission to intensive care units. Myotoxicity did not occur in any patient who received early (within six hours) tiger snake antivenom but occurred in 20% of those who had late or no antivenom.[10] (The use of tiger snake, rather than black snake, antivenom for red-bellied black snake is a long-standing practice which is supported by neutralisation studies but not, as yet, clinical trials.) The implication of this research is that antivenom should perhaps be used more often (and early) in red-bellied black snake envenomation.

In addition, an anticoagulant coagulopathy occurred in the majority (61%) of envenomed patients (although no patients developed life-threatening haemorrhage). An abnormal activated partial thromboplastin time could therefore be used as an early indicator of those patients with systemic envenoming. One vial of tiger snake antivenom should be considered for these patients.[10]

There is a note of caution to be sounded as hypersensitivity reactions occurred in over one-third of all antivenom administrations. This problem is common with tiger snake (as well as death adder and polyvalent) antivenom.[11] An ongoing trial (ACTRN12611000588998) is examining the clinical harm–benefit of using antivenom to treat envenomation by the red-bellied black snake.

Redback spider

The question of efficacy versus effectiveness has also been raised for other Australian antivenoms. Redback spider antivenom has always been recommended for intramuscular injection.[3] However, large molecular weight antibodies would be expected to have very slow systemic absorption after intramuscular injection. An efficacious antivenom would be clinically ineffective if it did not rapidly reach the site of venom action.[2] To test this hypothesis there have been two randomised controlled trials of intravenous versus intramuscular antivenom for redback spider envenoming.[12,13] Both showed no difference in outcome between the routes of administration. In one trial,[13] antivenom concentrations were measured showing that antivenom (as

Analgesia is the mainstay of treatment for redback spider bite

Fig. 2 **Red-bellied black snake**

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Fig. 3 **Redback spider**

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predicted) could only be detected in blood after intravenous administration.[14] As intravenous doses were not more clinically effective, this casts doubt on whether redback antivenom has any clinically meaningful benefit. A placebo-controlled trial of intravenous antivenom (ACTRN12609000063213) is currently underway.

As clinical effectiveness of the antivenom has yet to be demonstrated, adequate analgesia becomes even more important in the management of redback spider bite. Most patients should have an opioid (for example oxycodone 5 mg) plus paracetamol (1 g) and/or a non-steroidal anti-inflammatory drug (for example ibuprofen 800 mg).

Box jellyfish

Box jellyfish antivenom is an example where the difference between in vitro efficacy and clinical effectiveness is extreme. Severe box jellyfish envenoming from *Chironex fleckeri* results in rapidly developing (10–20 minutes) cardiovascular compromise and cardiac arrest. Although the antivenom is widely stocked in northern Australia, there have been at least four deaths despite antivenom administration. Conversely there has been survival after cardiac arrest, without antivenom, when cardiopulmonary resuscitation has been early and effective.[15]

The antivenom is efficacious in that pre-mixing it with venom before injecting the combination prevents cardiovascular collapse in rats.[16] However, the antivenom was not effective in preventing cardiovascular collapse when administered after the venom and was not effective even when the antivenom was infused before the venom.[16] This suggests that the onset of the cardiac toxicity is much more rapid than the binding of antivenom to venom.[2]

Snake antivenoms lack specificity

The horses used to develop the antivenoms are each injected with venoms from all major groups of snakes. Monovalent antivenoms are then formulated to contain sufficient antivenom to neutralise the average amount of venom obtained from milking the snake named on the label. This means that 'monovalent antivenoms' also contain large amounts of antibodies to all families of snakes, regardless of what is stated on the label.[17-19] The exception to this is sea snake antivenom and envenomation. No other monovalent or even polyvalent antivenom provides antibodies raised against sea snake venom and only the specific monovalent antivenom is likely to be useful.[20]

It is preferable to use the correct monovalent antivenom for treatment, but there is some leeway for clinicians. For example, if the type of snake is unknown but the clinical syndrome or geography is most consistent with just one or two snakes, then it is reasonably safe to use monovalent antivenom(s) rather than polyvalent antivenom. Alternatively, if a patient is seriously envenomed by an Australian snake but supplies of the specific monovalent antivenom are not available at that hospital, it is preferable to give the patient whatever monovalent snake antivenom is available rather than delay treatment.

Conclusion

For most Australian snake bites the treatment of envenomation is one vial of antivenom. The antivenom should be appropriate for the family of snakes suspected to have caused the bite.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. The dose of antivenom used to treat a snakebite is determined by the effect of envenomation on coagulation.

6. Patients who develop envenomation after being bitten by a red-bellied black snake can be treated with tiger snake antivenom.

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FURTHER READING

Toxicology and Wilderness Expert Group. Therapeutic guidelines: toxicology and wilderness. Version 2. Melbourne: Therapeutic Guidelines Limited; 2012.

Book review

Community pharmacy: symptoms, diagnosis and treatment. Australia and New Zealand edition. 2nd edition.

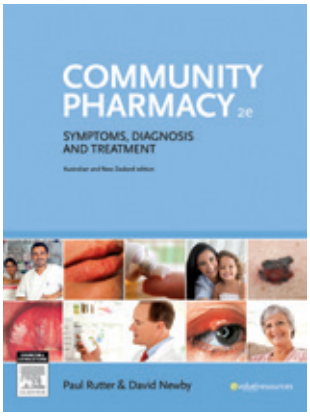
Rutter P, Newby D.
Sydney: Churchill Livingstone Australia; 2011.
360 pages
Price: $115

This is a book on pharmacy primary care written in the context of Australian and New Zealand practice. Topics covered include common respiratory and gastrointestinal disorders, ophthalmology and otic conditions, skin conditions, soft tissue injury, women's health and common conditions affecting paediatrics. There is an introductory chapter on communication skills and patient assessment.

Each chapter is well presented starting with the prevalence, aetiology, signs and symptoms of the conditions, followed by questions to ask in patient assessment, treatment options, contraindications to these treatments, and general self-management advice. There is a reference section at the end of each chapter if you decide to probe further into the topics. This book also has a good chapter on the supply of emergency contraception, motion sickness medications, nicotine replacement therapy, and weight loss products. The authors also incorporate a range of up-to-date evidence for the various treatments from the Cochrane Collaboration, Australian Medicines Handbook, Medicines Safety Update (formerly the ADRAC Bulletin), Therapeutic Guidelines, Food and Drug Administration and from research publications.

Some information is inconsistent with other resources. An example of this is the advice to avoid the use of applicators in the treatment of vaginal thrush in pregnant women even though the Australian Medicines Handbook 2012 states that vaginal applicators may be used with care in pregnancy. Another example is the recommendation on threadworm treatment where all family members of an infected person need to be treated at the same time. The Australian Medicines Handbook states that treatment of other family members is only necessary if infection is not eradicated.

Overall, this book is a great reference in the pharmacy. It could be a useful textbook for pharmacy students if you are after a concise compilation of essential information on a range of primary health conditions manageable in a pharmacy.



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