Review

Antivenom efficacy or effectiveness: The Australian experience

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A B S T R A C T

Despite widespread use of antivenoms, many questions remain about their effectiveness in the clinical setting. The almost universal acceptance of their value is based mainly on in vitro studies, animal studies and human observational studies. Numerous examples exist where they demonstrate clear benefit, such as consumption coagulopathy in viper envenoming, prevention of neurotoxicity in Australasian elapid bites, systemic effects in scorpion and funnel-web spider envenoming. There are also concerns about the quality and efficacy of some antivenoms. However, it is important not to confuse the efficacy of antivenom, defined as its ability to bind and neutralise venom-mediated effects under ideal conditions, and the effectiveness of antivenom, defined as its ability to reverse or prevent envenoming in human cases. There are numerous potential reasons for antivenom failure in human envenoming, of which antivenom inefficacy is only one. Other important reasons include venom-mediated effects being irreversible, antivenom being unable to reach the site of toxin-mediated injury, or the rapidity of onset of venom-mediated effects. A number of recent studies in Australia bring into question the effectiveness of some antivenoms, including snake antivenom for coagulopathy, redback spider and box jellyfish antivenoms. Despite brown snake antivenom being able to neutralise venom induced clotting in vitro, use of the antivenom in human envenoming does not appear to change the time course of coagulopathy. However, it is important that apparent antivenom inefficacy in specific cases is correctly interpreted and does not lead to a universal belief that antivenom is ineffective. It should rather encourage further studies to investigate the underlying pathophysiology of envenoming, the pharmacokinetics of venoms and antivenoms, and ultimately the effectiveness of antivenom based on snake type, clinical effects and timing of administration.

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Despite widespread use of antivenoms over the last century (Hawgood, 1999), many questions remain about their effectiveness in the clinical setting (Currie, 2006). There is a common perception that they are highly effective for the majority of envenoming conditions. In fact, there is limited evidence to support this and the almost universal acceptance of their value is based mainly on in vitro studies, animal studies and observational studies in humans.

1. Venoms and antivenoms

Venomous animals have specialized glands and venom apparatus to produce venom and inject or apply it parenterally into other organisms (Meier, 1995). This contrasts to poisonous animals which lack this specific apparatus and usually have to be ingested to cause toxic effects (Isbister and Kiernan, 2005). Envenoming
syndromes most commonly and importantly result from bites or stings by venomous snakes, scorpion, spiders and marine creatures. Venom consists of a mixture of toxins which have a broad range of toxic effects in vitro and in vivo. When injected into humans (or animals) these toxins produce unique clinical syndromes. The most important toxins from a clinical perspective include neurotoxins (Isbister and Kiernan, 2005; Kuruppu et al., 2008; Nicholson and Graudins, 2002), haemorrhagins (Hati et al., 1999), coagulant toxins (Isbister, 2009), myotoxins (Mebas and Ownby, 1990) and necrotoxins (Goddard and Ilia, 1998).

Antivenoms are antibody preparations that are produced from the plasma of animals, usually horses or sheep, by injecting the animals with venom (Gutierrez and Rucavado, 2000; Vetter and Isbister, 2008). Antivenoms are antibody preparations that are produced from the plasma of animals, usually horses or sheep, by injecting the animals with venom (Gutierrez and Rucavado, 2000; Vetter and Isbister, 2008). The review will contrast the efficacy of antivenom, defined here as its ability to bind and neutralise venom-mediated effects under ideal conditions (in vitro studies and animal studies of binding and neutralisation), and the effectiveness of antivenom, defined as its ability to reverse or prevent envenoming in human patients.

Over the last decade there have been significant concerns about the availability and quality of snake antivenoms (Lalloo et al., 2002), mainly in the rural tropics where the burden of disease is the greatest. Much of the debate has focused on the quality and efficacy of antivenoms, and therefore on whether antivenom manufacturers are producing high quality and efficacious antivenoms. These concerns about snake antivenom are under-pinned by a strong belief that if antivenoms are manufactured correctly, they will be effective for most snake bites. Suggestions have been made as to whether some antivenoms in fact neutralise (or bind) to specific important toxins in the venom and their inability to do this has resulted in antivenom failure in the clinical setting (Lalloo and Theakston, 2003). The idea that snake antivenom may not actually be clinically effective is rarely entertained. Interestingly, the belief in antivenom effectiveness is less clear for scorpion antivenoms, where there is far more debate about whether antivenoms are beneficial in the clinical setting (Abroug et al., 1999; Amaral and Rezende, 2000; Gueron and Ilia, 1999).

There are limited well designed and very few placebo randomised controlled trials of antivenom effectiveness (Abroug et al., 1999; Boyer et al., 2009; Lalloo and Theakston, 2003). Numerous preclinical and in vitro studies have demonstrated that antivenoms can bind venoms and prevent appropriate venom-mediated effects in vitro if pre-mixed with venom (Graudins et al., 2001; Isbister et al., 2007b; Ismail and Abd-Elsalam, 1998; Laing et al., 2004; Rosas-Cerrillo et al., 2008; Winter et al., 2009). For some venom-mediated effects there are clinical studies which support antivenom being an effective treatment. Studies have shown effectiveness of antivenom for venom induced consumption coagulopathy (VICC) in West African saw-scaled viper (Echis carinatus) and Russell’s viper envenoming (Myint et al., 1985; Warrell et al., 1977). For neurotoxicity there are studies demonstrating antivenom effectiveness in taipan (Oxyuranus crinitus) bites in Papua New Guinea (Currie, 2006; Lalloo et al., 1995a; Trevett et al., 1995), scorpion envenoming (Boyer et al., 2009; Calderon-Aranda et al., 1995), and funnel-web spider envenoming (Hartman and Sutherland, 1984). Conversely, other studies have demonstrated that for at least some effects, antivenom appears to have a much more limited role, such as delayed use in neurotoxicity (Kularatne, 2002; Phillips et al., 1988; Pochanugool et al., 1997; Theakston et al., 1990), VICC in Australian elapid envenoming (Isbister et al., 2009; Tanos et al., 2008), myotoxicity, renal failure (Myint et al., 1985) and local tissue effects (Dart et al., 2001; Warrell et al., 1976, 1977). Although a number of randomised controlled trials of antivenom have been undertaken (Ariaratnam et al., 2001; Dart et al., 2001; Isbister, 2006; Isbister et al., 2008b; Otero et al., 2006; Paul et al., 2004; Smalligan et al., 2004), the majority compare types of antivenoms, antivenom dose or route of administration, and are not placebo controlled trials. The few placebo controlled trials have mainly been with scorpions and have not been universally supportive of

<table>
<thead>
<tr>
<th>Antivenom inefficacy</th>
<th>The inability of the antibodies in the antivenom to bind the toxins in the venom. This appears to be rare.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irreversible venom-mediated effects</td>
<td>Toxin injury that is irreversible such as pre-synaptic neurotoxicity (nerve terminal destruction) (Kuruppu et al., 2008), myotoxicity or renal injury (Isbister et al., 2007a).</td>
</tr>
<tr>
<td>Inability of antivenom to reach venom target</td>
<td>This can occur with venom-mediated injury at the bite site or when toxin molecules are much smaller than antivenom molecules (e.g. short chain neurotoxins compared to IgG molecules) (Chippaux and Goyffon, 1998).</td>
</tr>
<tr>
<td>Rapid venom onset</td>
<td>Rapid onset of envenoming such that antivenom is unable to prevent or reverse severe or life-threatening effects, such as in cardiac toxicity from box jellyfish (Winter et al., 2009).</td>
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<tr>
<td>Mismatch of venom and antivenom pharmacokinetics</td>
<td>This will manifest as “recurrence” and is thought to occur when there is ongoing venom absorption after antivenom has been eliminated. This is usually only a problem with the rapidly eliminated Fab type antivenoms (Boyer et al., 2001).</td>
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the effectiveness of antivenom (Abroug et al., 1999; Boyer et al., 2009).

There are numerous potential reasons for the failure of antivenom in cases of human envenoming, of which antivenom ineffectiveness, i.e. the inability of the antibodies to bind the toxins in the venom, is only one. Other important reasons include venom-mediated effects being irreversible (e.g. presynaptic neurotoxicity), antivenom being unable to reach the site of toxin-mediated injury or the rapidity of the onset of venom-mediated effects (Table 1 and Fig. 1). It is also important to consider whether the reasons for antivenom failure differ for different antivenoms and more importantly whether they differ based on particular venom-mediated clinical effects. Making the assumption that antivenom efficacy always implies antivenom effectiveness, may lead to the belief that poor clinical response to antivenom is in fact antivenom ineffectiveness or have low potency, and therefore in some cases to escalating doses of antivenom being used with no benefit (Isbister et al., 2008b; Yeung et al., 2004).

The efficacy of a number of Australian antivenoms has been questioned over the last two decades (Currie, 2003; Madaras et al., 2005; Masci et al., 1998; Sprivulis et al., 1996; Tibballs and Sutherland, 1991; Yeung et al., 2004). This has resulted in significant increases in antivenom dose for most snake antivenoms (Yeung et al., 2004) and redback spider antivenom (Ellis et al., 2005; Isbister et al., 2008b), which has the potential to increase antivenom reaction frequency (Isbister et al., 2008a) and is extremely costly. Australian antivenoms will be used as examples to explore whether poor clinical response to antivenom is in fact antivenom efficacy or antivenom effectiveness.

3. Australian brown snake (*Pseudonaja* spp.) antivenom

Significant concerns have been raised over the efficacy of brown snake (*Pseudonaja* spp.) antivenom in Australia because a number of animal and laboratory studies suggested that the commercial antivenom was poorly able to neutralise the prothrombin activator component of the venom (Madaras et al., 2005; Masci et al., 1998; Sprivulis et al., 1996; Tibballs and Sutherland, 1991). It was then suggested that this was the reason for antivenom failure in some cases of human envenoming (Henderson et al., 1993) and the requirement for much larger doses of antivenom to treat patients in some parts of Australia (Yeung et al., 2004). Over a period of a decade this lead to increasing doses of antivenom being administered for brown snake envenoming (Currie, 2000) and recommendations in some parts of Australia for an initial dose of 10 vials of brown snake antivenom (Yeung et al., 2004) compared to the original one vial recommended by the manufacturer (White, 2001). A critical examination of these earlier studies and consideration of recent laboratory and clinical studies (Isbister et al., 2006, 2007b; O'Leary et al., 2006) now shows that this is unlikely to be the case and that brown snake antivenom is highly efficacious.

Sprivulis et al. (1996) investigated the ability of Australian snake antivenom to prevent the in vitro procoagulant clotting effects of their respective venoms. The study used very high venom concentrations based on the assumption that the venom concentration in patients can be simply calculated from the average venom yield of the snake. In these series of experiments they were unable to prevent brown snake venom induced clotting in vitro with a range of increasing concentrations of antivenom and required much larger amounts of the other antivenoms for their respective venoms (Sprivulis et al., 1996). The investigators suggested that even 25 times the recommended amount of antivenom (1 vial) was insufficient to prevent clotting for brown snake. An earlier study by Tibballs and Sutherland (1991) using brown snake venom and antivenom showed that 10–25 times the recommended dose of antivenom was required to prevent coagulation abnormalities using 10 μg/kg of venom (similar amount to Sprivulis et al.). The problem with both of these studies (Sprivulis et al., 1996; Tibballs and Sutherland, 1991) was that the very high venom concentrations used were not consistent with concentrations that have now been measured in envenomed patients, even those with severe envenoming (Isbister et al., 2007b). The amount of venom administered would result in a blood concentration approximately 100–1000 times that seen in patients, so the fact that Tibballs et al. demonstrated some effect of antivenom at 10–25 times the recommended dose is in fact reassuring that the recommended dose of 1 vial is more than sufficient.

The laboratory studies by Sprivulis et al. (1996) and Tibballs and Sutherland (1991) introduced the idea of poor antivenom efficacy and that larger doses may be required for treatment. A number of observational studies appeared to confirm this (Barrett and Little, 2003; Isbister and Currie, 2003; Yeung et al., 2004) and a study of brown snake bites in Western Australia recommended an initial dose of 10 vials of antivenom based on the reports of increasing doses being used in patients (Yeung et al., 2004). The problem with these studies was that they reported the amount of antivenom being given, rather than objectively assessing the effectiveness of antivenom. The crucial error was that recovery from VICC, the major indication for antivenom in Australia, takes up to 12–18 h to occur after antivenom administration (Isbister et al., 2006, 2009). Early testing of clotting function before improvement could be expected, based on the pathophysiology of consumption of clotting factors and the required re-synthesis, was resulting in inappropriate repeat antivenom dosing. These observational studies were therefore simply reporting the inappropriate use of large antivenom doses and not assessing antivenom dose.
A more recent study by our group using similar clotting studies demonstrated that the equivalent of one vial of antivenom is sufficient to prevent the in vitro procoagulant effect of brown snake venom (Fig. 2) (Isbister et al., 2007b). This is based on using clinically relevant concentrations of venom (4–95 ng/mL), determined from a study of patients with brown snake envenoming (Isbister et al., 2007b; O’Leary et al., 2006). The same study also showed that antivenom concentrations equivalent to the administration of one vial of antivenom were able to bind all free venom in solution at venom concentrations equivalent to those seen with human envenoming (Isbister et al., 2007b). These studies provide significant evidence of antivenom efficacy in vitro, both binding to venom and preventing venom-induced clotting, and demonstrate the importance of undertaking in vitro studies that are clinically relevant. Based on these studies (Isbister et al., 2007b) an initial dose of brown snake antivenom should be 1 vial and repeat doses are not required, and it will take 12–18 h for the coagulopathy to recover.

Concerns have also been raised about the efficacy of tiger snake antivenom. In the study by Sprivilus et al. (1996) large doses of antivenom were required to prevent the in vitro procoagulant effect of the relevant venoms. However, similar to brown snake venom, very high venom concentrations were used, about 1000-fold those expected in human envenoming (O’Leary et al., 2008), which are again not clinically relevant. Preliminary studies of tiger snake envenoming show that venom concentrations in patients are also in the range 5–200 ng/mL (O’Leary et al., 2008) and that tiger snake antivenom is able to prevent the procoagulant effect of tiger snake venom in vitro (O’Leary et al., 2007).

The use of very large amounts of venom for in vitro assays to test antivenom efficacy is a major problem as described above. Similar issues have arisen when drugs have been used at much higher concentrations for in vitro studies compared to those seen in human studies (Zar et al., 1982). This underlies the importance of undertaking observational studies of human envenoming where serial venom concentrations are measured. Such studies are essential to not only make sure that clinically appropriate venom concentrations are used for in vitro studies but provide an understanding of the time course and likely reversibility of venom-mediated effects. Fig. 2 compares in vitro clotting studies done at clinically relevant concentrations, to those used by Sprivilus et al., which are 1000 times those seen in envenomed patients.

4. Failure of antivenom in recovery from VICC in Australian snakebite

A semi-mechanistic systems model of the coagulation pathway has recently been developed that explored the effects of taipan venom on the coagulation pathway (Tanos et al., 2008). The model was able to simulate clotting factor information consistent with data obtained from actual taipan bites (Lalloo et al., 1995b). However, the model also suggested that antivenom neutralisation needs to occur soon after venom enters the circulation to have an impact on the recovery of the coagulopathy (Tanos et al., 2008). This has concerning implications for antivenom therapy in VICC in Australian snakebite, because it suggests that it may not have any effect on the coagulopathy if given more than an hour after the bite.

This had already been reported for the coagulopathy in taipan bite in Papua New Guinea, where early antivenom did not result in a more rapid recovery of the coagulopathy (Lalloo et al., 1995a). Further empirical support for this has recently been produced for the coagulopathy resulting from bites by brown snakes and tiger snakes in Australia (Isbister et al., 2009). This study was unable to demonstrate any relationship between the timing of antivenom and the recovery of the coagulopathy (Isbister et al., 2009), suggesting that antivenom may not play a role in speeding the recovery of VICC in Australia.

The above research and earlier studies question the commonly held belief in Australia that antivenom is effective for VICC but not for presynaptic neurotoxicity (White, 2001). The administration of antivenom within 6 h of the bite in taipan envenoming appears to reduce the number of patients requiring endotracheal intubation (Lalloo et al., 1995a), whereas the administration of antivenom does not change the course of the coagulopathy (Lalloo et al., 1995a; Tanos et al., 2008).

5. Other Australian antivenoms

Problems with antivenom effectiveness in Australia are not limited to snake antivenoms and there are concerns about the effectiveness of both box jellyfish and redback spider antivenom.

Chironex fleckeri, the major Australian box jellyfish, has caused over 70 deaths and continues to be responsible for paediatric deaths.
in the north of Australia. Severe envenoming occurs with large areas of tentacle contact with skin and results in rapidly developing (10–20 min) cardiovascular compromise and cardiac arrest due to a lethal toxin. An ovine antivenom was developed against box jellyfish venom and has been used over the last thirty years with questionable success. There have been at least four deaths despite antivenom administration. Protagonists of the antivenom have attributed survival in cases where antivenom was used. However, similar patients survived prior to the introduction of antivenom with early and effective cardiopulmonary resuscitation, making it unclear what role antivenom has (Currie, 2003; Currie and Jacups, 2005). Like snake antivenoms, this has led to the idea of poor antivenom efficacy and the suggestion that specific antibodies were missing to the lethal toxin (Currie, 2003; Ramasamy et al., 2004).

Two recent studies have investigated the efficacy of box jellyfish antivenom in its ability to bind and neutralise the venom (Konstantakopoulos et al., 2009; Winter et al., 2009). Western blot analysis using box jellyfish antivenom or antibodies raised to the venom preparation showed that both could detect the majority of the protein bands in the venom ranging from 10 to 200 kDa (Winter et al., 2009). Pre-mixing antivenom (and antibodies) with the venom prevented toxicity in a cell-based assay (Konstantakopoulos et al., 2009) and also prevented cardiovascular collapse in an in vivo rat model (Winter et al., 2009). However, administration of the antivenom after venom addition in the in vivo rat model did not prevent cardiovascular collapse. Even more concerning still, administration of antivenom to the rat prior to venom (not pre-mixed with venom) also did not prevent cardiovascular collapse (Winter et al., 2009). These experiments do not support the idea that there are antibodies missing to the lethal component, and show that the antivenom is in fact highly efficacious. However, they also demonstrate that antivenom is highly unlikely to be effective in the clinical setting because even if antivenom was administered prior to the box jellyfish sting, it would not be effective. It is unclear why prior administration of antivenom is not effective, but may simply be due to the rapidity of onset of venom-mediated cardiovascular collapse.

Redback spider antivenom is the most commonly used antivenom in Australia and has been routinely used for the treatment of systemic effects and pain in redback spider envenoming. However, there is limited evidence to support its effectiveness (Wiener, 1961), and over the last decade its use via the intramuscular route has been questioned, because of reported treatment failures (Isbister, 2002). This has lead to two randomised controlled trials of intravenous versus intramuscular antivenom for redback spider envenoming being undertaken (Ellis et al., 2005; Isbister et al., 2008b). Both of these trials showed no difference between the routes of administration (Ellis et al., 2005; Isbister et al., 2008b) but in the second trial (Isbister et al., 2008b), antivenom concentrations were measured showing that antivenom could only be detected in blood after intravenous administration (Isbister et al., 2008c). The negative results of the two trials could be interpreted as both routes of administration being equally effective. However, in light of the pharmacokinetic data, it seems more likely that the two routes of administration are in fact equally ineffective, thus questioning the effectiveness of redback spider antivenom per se. A placebo controlled trial is currently underway to test the hypothesis that redback antivenom is not effective.

6. Implications of antivenom efficacy without effectiveness

It is important that apparent antivenom ineffectiveness in specific cases is correctly interpreted and does not lead to a universal belief that antivenom is ineffective. This research should encourage further studies to understand the underlying pathophysiology of envenoming, the pharmacokinetics of venoms and antivenoms and ultimately the effectiveness of antivenom based on snake species, clinical effects, as well as dose, route, and timing of antivenom administration. An important example is the obvious difference between the consumptive coagulopathy in Echis spp. (carpet vipers) from Africa, and Australasian elapid snakes. There is good evidence from observational studies that the coagulopathy in Echis spp. bites may last for many days untreated, but will resolve a mean of 12 h after antivenom treatment (Warrell et al., 1977). It is unclear why there is persistent coagulopathy for Echis spp. but not Australasian elapids, but it underlies the importance of assessing antivenom in each clinical scenario.

In Australia, funnel-web spider antivenom provides an important contrast to those discussed so far. Although funnel-web spider envenoming is rare in Australia it is potentially fatal and continued to cause deaths in the late 1970s, despite care in modern intensive care units (Isbister et al., 2005). Although no controlled trial of the funnel-web spider antivenom was undertaken the dramatic response in the first few cases of severe envenoming, particularly in young children, provided strong evidence that the antivenom was effective against the neurotoxicity (Hartman and Sutherland, 1984). With the introduction of antivenom there has been a significant decrease in reports of severe envenoming requiring intensive care admission, decreased lengths of stay and no reports of multi-organ failure (Isbister et al., 2005).

Conflicts of interest

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