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Antivenom cross neutralisation in a suspected Asian pit viper envenoming causing severe coagulopathy

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ABSTRACT

There is evidence of cross-neutralisation between common toxin groups in snake venoms and therefore the potential for antivenoms to be effective against species they are not raised against. Here we present a 49 year old female bitten by an unknown pit-viper in Nepal. She developed a venom induced consumption coagulopathy with an unrecordable international normalised ratio and undetectable fibrinogen. On return to Australia 5 days post-bite she was treated successfully with one antivenom raised against Malayan pit viper and green pit viper venoms (Haemato-polvalent antivenom from Thailand) and then subsequently with another antivenom raised against American pit-viper venoms (Antivipmyn). Presumed pit viper venom was detected in patient sera with an enzyme immunoassay against *Hypnale hypnale* venom. There was increased absorbance before antivenom compared to non-envenomed control samples, which then decreased after the administration of each antivenom. The recurrence of venom detected by enzyme immunoassay between antivenom doses was accompanied by a recurrence of the coagulopathy. Cross reactivity between the unknown venom and both antivenoms was supported by the fact that no venom was detected in the pre-antivenom samples after they were incubated in vitro with both antivenoms. This case and investigation of the venom and antivenoms suggest cross-neutralisation between pit vipers, including pit vipers from different continents.

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1. Introduction

Snake envenoming is a neglected tropical disease causing significant mortality in morbidity in resource poor countries, mainly in the rural tropics (Kasturiratne et al., 2008). A major problem is the limited number of antivenoms available and many countries relying on other regions to manufacture antivenoms. With such a shortage of antivenom it is increasingly clear that other approaches are required to make antivenom more affordable, effective and accessible in many countries. One such approach is to focus on the cross-neutralisation of antivenoms and to develop antivenoms against common toxins in snake venoms (Wagstaff et al., 2006). Such cross-neutralisation has been demonstrated for Australian snake antivenoms (Isbister et al., 2010), for African snakes (Wagstaff et al., 2006), American snakes (Buschek et al., 2010) and Asian snakes (Leong et al., 2014; Tan et al., 2011). This potentially means that antivenoms developed in one country may be effective in other countries with snakes with similar toxin groups (Buschek et al., 2010).

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Many countries in Asia do not produce their own antivenoms and either have no antivenom available or rely on antivenoms made in other countries, principally Thailand, India, China and Taiwan. Although these antivenoms may be effective and it is more cost-effective to buy in antivenom from other countries, there needs to be pre-clinical and clinical studies to support the efficacy and effectiveness of antivenoms in different regions. A major issue in many parts of Asia is that antivenoms have not been raised against many of the Asian pit vipers, including hump-nosed viper (*Hypnale* spp.) and many *Trimeresurus* spp. A previous study has shown that antivenom raised against Malayan pit viper (*Calloselasma rhodostoma*) venom does cross-neutralise Hump-nosed viper venoms (Tan et al., 2011).

Here we present a case where a patient bitten by an unknown pit-viper in Nepal was treated successfully with one antivenom raised against Malayan pit-viper venom and then subsequently with another antivenom raised against American pit-viper venoms. Further in vitro studies demonstrated cross-reactivity and cross-neutralisation between the venom from this unknown pit viper from Asia, hump-nosed viper and Malayan pit-viper, and antivenoms made in Asia and the Americans.

2. Case

A 49-year-old previously well Australian female holidaying in Pokhara, Nepal, was bitten by a snake on the dorsum of the right foot late in the evening while getting into a car. She subsequently attended two hospitals in Nepal over the next 24 h for bite site pain and right leg swelling. At the time of her presentations, there were no symptoms of neurotoxicity or evidence of spontaneous or abnormal bleeding. Her medical notes from the second hospital she visited documented fang marks on the dorsum of her right foot with swelling of the right lower leg but no bruising (Fig. 1). Her observations were within normal limits and her neurological examination was documented as normal. Investigations performed were a chest radiograph which was normal, full blood count [FBC] (white cell count, 13×10^{-9}; haemoglobin [Hb], 133 g/L; platelets, 215×10^{-9}), prothrombin time was unrecordable (no clot formed), biochemistry was normal, and urinalysis was normal. A diagnosis of snakebite with coagulopathy was made and she was advised admission to hospital and the need for antivenom, which was documented as not currently available in Nepal. She was given vitamin K, penicillin and analgesia before deciding to discharge herself and return home to Australia for treatment.

Upon return to Australia the patient noticed new bruising to her legs from minor trauma in addition to ongoing pain and swelling of the right leg. On day five post bite she attended her local doctor who ordered investigations including coagulation tests which demonstrated a severe coagulopathy with an international normalised ratio (INR) >10, activated partial thromboplastin time (aPTT) >200s, fibrinogen <0.2 g/L (reference range [RR]: 1.7–4.5 g/L) and an elevated D-Dimer 15.1 mg/L (RR < 0.5 mg/L). Her FBC was normal with a Hb, 133 g/L and platelets, 174×10^{-9}. Biochemistry including renal and liver function was normal. She was referred to hospital the following day and on admission, an unrecordable INR and undetectable fibrinogen were confirmed. Further coagulation factor studies (II, V, VII, VIII and X) were done and were within the normal limits suggesting a thrombin like enzyme effect. She remained systemically well but had new bruising from minor trauma as well as persistent pain around the bite site and lower leg swelling. The geographical location of the bite and the probable presence of a thrombin-like enzyme in the venom suggested an Asian pit-viper. The only antivenom against an Asian pit-viper available in Australia was Haemato-polyvalent snake antivenom (Thai Red Cross Society, Bangkok, Thailand). This was obtained from Monash Venom Group, Monash University in Melbourne on day 7 post bite and two vials were administered over 30 min. Prior to antivenom her coagulation profile was unchanged with unrecordable INR, aPTT and fibrinogen. Four hours post antivenom her INR was 1.4 and aPTT was 22s with a fibrinogen of 0.2 g/L. Her fibrinogen continued to rise over the next 24 h to 0.5 g/L. However, over the next 36 h the fibrinogen dropped to <0.2 g/L and the INR and aPPT became unrecordable again on day 10 post bite. Her clinical state remained unchanged (Fig. 2).

Fig. 1. Photograph of the bite site taken on the day of the bite.

The recurrence of coagulopathy prompted another search for antivenom, but the only available antivenom against any pit-viper venom was Antivipmyn (Instituto Bioclon S.A. de C.V, Mexico) which was sourced from a reptile park in Gosford, New South Wales. Although this antivenom was raised against American pit-vipers, it was believed it might have some cross-reactivity and the potential benefit was felt to outweigh the risks. On day 10 post bite the patient was administered eight vials of Antivipmyn over 4 h. Prior to antivenom her INR, aPTT and fibrinogen were unrecordable. The following morning on day 11 post bite her INR was 1.3, aPTT 26s and fibrinogen 0.4 g/L. Her fibrinogen continued to rise to 1.3 g/L with an INR of 1.0 and aPTT of 23s on day 13 when she was discharged from hospital (Fig. 2). On phone

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