TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (2001) 95, 74–80

An open, randomized comparative trial of two antivenoms for the treatment of envenoming by Sri Lankan Russell's viper (*Daboia russelii russelii*)

C. Ariaranee Ariaratnam[1], Lena Sjöström[2], Zeenia Raziek[1], S. Abeyasinghe M. Kularatne[3], R. W. K. Kodikara Arachchi[3], M. H. Rezvi Sheriff[1], R. David G. Theakston[4] and David A. Warrell[5] *[1]Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka; [2]Protherics PLC, Macclesfield, UK; [3]Anuradhapura General Hospital, Anuradhapura, Sri Lanka; [4]World Health Organization Collaborating Centre for the Control of Antivenoms and Venom Research Unit, Liverpool School of Tropical Medicine, Liverpool, UK; [5]Centre for Tropical Medicine, University of Oxford, Oxford, UK*

Abstract

Russell's viper (*Daboia russelii russelii*) is an important cause of morbidity and mortality in Sri Lanka. In a study in 1985, Haffkine equine polyspecific antivenom in doses up to 20 g proved ineffective in clearing antigenaemia and caused a high incidence of anaphylactoid reactions. A new, monospecific ovine Fab-antivenom (PolongaTAb™) has been developed against the venom of Sri Lankan Russell's viper and, to assess its safety and efficacy, we carried out (in 1997) an open, randomized comparison of this with the Haffkine antivenom currently in use in the country. Patients with systemic envenoming following Russell's viper bite were randomized to receive an initial intravenous dose of either 1 g of PolongaTAb ($n = 23$) or 10 g of Haffkine antivenom ($n = 20$). One dose of PolongaTAb permanently restored blood coagulability in only 9 (41%) of 22 patients and 13 needed repeated doses, whereas the majority (14/20; 70%) had restored coagulability after 1 dose of Haffkine antivenom. There was a tendency towards more rapid resolution of local swelling and systemic manifestations in the Haffkine group. Venom antigenaemia was eliminated more quickly in the Haffkine group and ovine Fab was cleared from the circulation more rapidly than equine $F(ab')_2$. To evaluate safety, patients were closely observed for adverse reactions. Following a severe reaction with Haffkine antivenom all subsequent patients in this group were treated prophylactically with hydrocortisone and chlorpheniramine. Despite this, the incidence of adverse reactions was significantly higher in the Haffkine group compared with the PolongaTAb group (81% compared with 48%) and 4 patients had a severe anaphylactic reaction in the former group. In conclusion, the new antivenom is safer than Haffkine antivenom but, to avoid repeated doses, an initial dose higher than 1 g is needed in the treatment of Sri Lankan Russell's viper envenoming. The safety of this larger dose is the subject of further studies.

Keywords: snakebite, envenoming, *Daboia russelii*, antivenoms, efficacy, adverse reactions, comparative study, clinical trial, Sri Lanka

Introduction

Russell's viper (*Daboia russelii russelii*), locally called *thith polonga*, is probably the most important of the 6 dangerously venomous snakes of Sri Lanka (DE SILVA & RANASINGHE, 1983). It caused 60% of all cases of snakebite with envenoming admitted to Anuradhapura General Hospital during 1995 (unpublished data). Bites are seasonal, peaking during late October to November and again in the spring when they can number several hundred per month in some regions. Russell's viper bite is an occupational hazard predominantly of the poor rice farmers throughout its geographical range. The clinical features of Russell's viper envenoming in Sri Lanka are different from those described in other countries. Common features to all regions are coagulopathy, spontaneous bleeding and acute renal failure; however, the Sri Lankan snakes also cause neurotoxicity (e.g., ptosis, external ophthalmoplegia, paralysis of muscles of deglutition and mouth opening), rhabdomyolysis (resulting in myoglobinuria) and intravascular haemolysis (causing haemoglobinuria) suggesting variation in the composition of the venom (PHILLIPS *et al.*, 1988). Local effects of envenoming are usually relatively mild, but swelling, blistering, bruising, necrosis and secondary infection may develop.

Sri Lanka has no indigenous antivenom production and relies on antivenom produced in India by the Haffkine Institute of Bombay and the Serum Institute of India, Pune, using venom of Indian snakes. These Indian antivenoms are $F(ab')_2$-based equine polyspecific antivenoms, raised against the venoms of Russell's vipers, common kraits (*Bungarus caeruleus*), cobras (*Naja naja*) and saw-scaled vipers (*Echis carinatus*) collected in India (THEAKSTON & WARRELL, 1991). A study in Anuradhapura in 1985 showed that doses of up to 20 g of Haffkine antivenom were inefficient in clearing Russell's viper venom antigenaemia and frequently caused anaphylactoid reactions (PHILLIPS *et al.*, 1988). There is therefore a need for effective and safe antivenom for treating Russell's viper bites in Sri Lanka. One important reason why Indian antivenom may be relatively ineffective is the geographical variation in venom composition and antigenicity, reflected in the case of Russell's viper by the clinically different manifestations of envenoming detailed above (WARRELL, 1989, 1997). Recently, a new antivenom has been produced (PolongaTAb™), which is a monospecific, ovine Fab fragment, manufactured by immunizing sheep with pooled venom from Sri Lankan Russell's vipers. This antivenom was first used in a preliminary dose-finding study of patients with Russell's viper bites in Sri Lanka in 1995. It was shown to possess strong neutralizing activity against procoagulant and haemorrhagic components of Sri Lankan Russell's viper venom in the majority of patients (ARIARATNAM *et al.*, 1999). Unfortunately 34% of these study patients had early reactions, possibly because this particular batch was a prototype antivenom, with a high residual content of Fc fragments. For the present study, a new batch of antivenom was therefore manufactured with high potency and greater purity by using ion-exchange chromatography. This purification method has previously been shown to improve antivenom specificity (GRANDGEORGE *et al.*, 1996). The present study, carried out in collaboration with the Sri Lankan Health Ministry, aimed to compare the efficacy and safety of the new monospecific Fab fragment antivenom with the Haffkine antivenom for the treatment of Sri Lankan Russell's viper bites.

Patients and Methods

This study was designed as an open, randomized comparison of PolongaTAb and Haffkine antivenoms

Address for correspondence: Professor D. A. Warrell, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford OX3 9DU, UK; phone +44 (0)1865 220968; fax +44 (0)1865 220984, e-mail david.warrell@ndm.ox.ac.uk