Toxicon 117 (2016) 13–21

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Prospective, consecutive case series of 158 snakebite patients treated at Savannakhet provincial hospital, Lao People's Democratic Republic with high incidence of anaphylactic shock to horse derived F(ab')$_2$ antivenom

Inthanomchanh Vongphoumy [a], Phankham Chanthilat [b], Phongmany Vilayvong [b], Joerg Blessmann [a, c, *]

[a] Provincial Health Department, Savannakhet, Lao Democratic People's Republic
[b] Provincial Hospital, Savannakhet, Lao Democratic People's Republic
[c] Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany

ARTICLE INFO

Article history:
Received 7 December 2015
Received in revised form
11 March 2016
Accepted 15 March 2016
Available online 16 March 2016

Keywords:
Lao PDR
Venomous snakebites
F(ab')$_2$ snake antivenom
Anaphylaxis

ABSTRACT

Snakebites are a seriously neglected public health problem in Lao PDR. Community-based cross-sectional surveys in two districts of Savannakhet province in Southern Laos revealed an incidence of up to 1105 snakebites per 100,000 persons per year. In contrast the number of snakebite patients treated in district and provincial hospitals are low. In order to improve health care for snakebite victims, antivenom was introduced to Savannakhet provincial hospital in July 2013 and medical staff has been trained in management of venomous snakebites at the same time. After the intervention the number of snakebite patients treated at the provincial hospital increased significantly from 4 patients in 2012 to 158 snakebite patients between July 2013 and November 2015. They were included into a prospective, consecutive case series. Median age was 32 years (range 1.5–70 years) and male-to-female ratio 2.2:1. Forty patients were bitten by Malayan pit vipers, 26 by green pit vipers, 24 by cobras, including 3 cases of venom ophthalmia, 5 by kraits, 8 by non-venomous species and in 55 cases the snake could not be identified. Forty-three out of 158 patients received horse derived F(ab')$_2$ antivenom from Queen Saovabha Memorial Institute (QSMI) in Bangkok. Twenty-three patients (53%) developed early adverse reactions (EARs) within one hour after antivenom administration, including 13 patients (30%) with severe anaphylaxis. This extremely high rate of severe EARs turns the use of antivenom into a risky intervention. In contrast a retrospective chart review from Chulalongkorn University in Bangkok found only 3.5% early reactions including 1.2% severe anaphylactic reactions using the same antivenom from QSMI between 1997 and 2006. The reason for this enormous difference remains unclear. A better understanding of the aetiology and pathophysiology behind antivenom induced anaphylaxis is crucial in order to identify patients at risk and to improve safety of antivenom administration.

1. Introduction

Due to subtropical and tropical climate, Laos has a rich snake fauna with 101 non-venomous and 23 venomous species described to date (Teynié and David, 2010). According to surveys in Thailand and preliminary experience in Laos, six snakes within 23 venomous species are responsible for the majority of venomous snakebites (Blessmann et al., 2010; Chanhome et al., 1998; Viravan et al., 1992; Vongphoumy et al., 2015). They are considered medically important venomous snakes and snake antivenom is available at Queen Saovabha Memorial Institute (QSMI) in Bangkok, Thailand. Envenoming caused by each of these six snakes results in significant morbidity and mortality (Wongtongkam et al., 2005a, 2005b). Two pit vipers, the Malayan pit viper (*Calloselasma rhodostoma*) and the green pit viper (*Trimeresurus albolabris*) cause severe local cytotoxic damage with swelling, blistering and necrosis. Procoagulants and

* Corresponding author. Bernhard Nocht Institute for Tropical Medicine, Bernhard Nocht Strasse 74, 20359 Hamburg, Germany.
E-mail address: J_Blessmann@yahoo.de (J. Blessmann).

http://dx.doi.org/10.1016/j.toxicon.2016.03.011
0041-0101/

other haematotoxic venom components induce severe coagulation disorder. Pre- and postsynaptic neurotoxins in the venom of 4 elapid snakes, the monocled cobra (*Naja kaouthia*), the king cobra (*Ophiophagus hannah*) the Malayan krait (*Bungarus candidus*) and banded krait (*Bungarus fasciatus*) cause muscle paralysis and death from respiratory failure, if appropriate medical care is not available. Cytotoxic components, including cardiotoxins in the venom of cobras contribute to morbidity and mortality by causing severe local cutaneous and subcutaneous tissue necrosis, cardiac arrhythmia, arterial hyper- and hypotension and heart failure.

Snakebites are a seriously neglected public health problem in Lao PDR. Community-based surveys revealed a high incidence of up to 1105 snakebites per 100,000 inhabitants per year in Savannakhet province in Southern Laos (Vongphoumy et al., 2015). In contrast the number of snakebite patients treated in provincial and district hospitals is very low, because most snakebite victims rely on traditional treatment in their villages and do not seek medical care in hospitals. Three main reasons explain this treatment seeking behaviour. Firstly snakebites affect predominantly poor people in remote communities and health care utilization is often a significant financial burden and a considerable number of people cannot afford it. Secondly the strong belief in the value and benefit of traditional treatment is widespread and has been shown for snakebites in a KAP-survey performed in one district in Savannakhet province, Lao PDR in 2013. According to this survey approximately 90% believe in the effectiveness of traditional medicine for snakebites (Khamphanthong, 2013). The third and most compelling reason is the fact, that snakebite patients with systemic envenoming won't get effective treatment in local health facilities, because knowledge of health care staff about management of venomous snakebites is not sufficient and antivenom the only effective treatment of systemic envenoming is not available (Vongphoumy et al., 2015).

In order to improve health care for snakebite victims, monospecific and polyspecific horse derived $F(ab')_2$ antivenom from QSMI in Bangkok was introduced at Savannakhet provincial hospital in July 2013 and medical staff was trained in management of venomous snakebites. After this intervention the number of patients with snakebites increased significantly from 4 patients admitted to Savannakhet provincial hospital in 2012 to 158 patients admitted between July 2013 and November 2015. A prospective, consecutive case series was conducted and clinical features, outcome, treatment and early side effects of antivenom administration, particularly the incidence of anaphylaxis of these 158 snakebite patients were documented.

2. Methods

2.1. Study population, documentation and follow-up

A prospective, consecutive case series of 158 snakebite patients was conducted at Savannakhet provincial hospital from July 2013 to November 2015. Name, age, sex, address, location of the bite site, snake species responsible for the bite, first aid applied, local and systemic symptoms of envenoming were documented on an admission sheet. A complete blood cell count was performed for every patient and prothrombin time plus the calculated INR for patients after viper bites or after bites from an unknown species. Those patients with systemic signs of envenoming received immediate treatment with the appropriate antivenom. Those patients with non-venomous snakebites confirmed by the snake brought along to the hospital received tetanus vaccination and were discharged. All other patients were followed for at least 24 h in the hospital for clinical and laboratory signs of neurotoxic or haematotoxic envenoming.

2.2. Reliability of snake identification

Identification of snake species or genus was considered reliable, if the patient brought the snake to the hospital. In case of green pit vipers and kukri snakes only the genus *Trimeresurus* or *Oligodon* respectively was identified. Snake identification by the victim or an accompanying person was considered reliable if the patient reported a Malayan pit viper, green pit viper, cobra or krait bite, and presented with local and/or systemic haematotoxic or neurotoxic signs of envenoming. However reliable identification for green pit vipers, cobras or kraits was restricted to the genus level. Snakes brought along to the hospital were identified by the study team and in cases of doubt a photo was send to Dr. Ulrich Kuch, at the university of Frankfurt, Germany.

2.3. Antivenom

Antivenoms from Queen Saovabha Memorial Institute (QSMI) in Bangkok, Thailand was used for patients in this case series. It is an equine, pepsin digested $F(ab')_2$ antivenom, fractionated by caprylic acid and the final product is lyophilized. The shelf life is 5 years and antivenom in the present case series were used within the first two years after manufacturing date. Seven monospecific and 2 polyspecific antivenoms against the medically important snakes in Thailand are available. One polyspecific formulation includes 3 haematotoxic snakes, Malayan pit viper (MPV) (*C. rhodostoma*), green pit viper (GPV) (*T. albolabris*) and Russell's viper (*Daboia russelii siamensis*) and the second polyspecific formulation includes 4 neurotoxic snakes, the common cobra *(Naja kaouthia)*, king cobra *(O. hannah)*, Malayan krait *(B. candidus)* and banded krait *(B. fasciatus)*. The Russell's viper (*D. russelii siamensis*) is found only in Central Thailand and not in Laos, but the other six snakes are responsible for most venomous snakebites in Lao PDR (Blessmann et al., 2010; Vongphoumy et al., 2015; Teynie and David, 2010). Monospecific green pit viper antivenom from QSMI produced with venom of *T. albolabris* is also effective against *Trimeresurus macrops* and *Trimeresurus popeiorum* envenoming and monospecific cobra antivenom produced with venom from *Naja kaouthia* is also effective against *Naja siamensis* envenoming, at least against the alpha-neurotoxin (Khow et al., 1997, Chanhome et al., 2002).

2.4. Indication for administration of antivenom and dosage

Monospecific antivenom for Malayan pit viper (*C. rhodostoma*), green pit viper (*T. albolabris*), cobra (*Naja kaouthia*), and Malayan krait (*B. candidus*) was administered if snake species or genus identification was considered reliable. Polyspecific haematotoxic antivenom or polyspecific neurotoxic antivenom was administered if the patient presented with either haematotoxic or neurotoxic signs of envenoming, but identification of the snake species was not possible. Criteria for indication of antivenom treatment for neurotoxic envenoming were any clinical sign of muscle paralysis like ptosis, any other signs of cranial nerve palsy, weakness of limbs, dyspnoea and hypoxia. Criteria for indication of haematotoxic envenoming were platelet count of less than 50,000/μl, INR >5 and/or clinical signs of bleeding.

The dosage of antivenom was based on the recommendation of the manufacturer, which are 3 vials for Malayan pit viper and green pit viper envenoming, 5 vials for Malayan krait envenoming and 10 vials for cobra envenoming. Based on previous experience in Lao PDR the dose for Malayan pit viper envenoming was increased to 4 vials in case of severe coagulation disorders with INR >10, platelet count <30,000/μl and/or clinical signs of bleeding (Blessmann et al., 2010). In case of less severe coagulation disorder after green pit viper envenoming with INR of 5–10, platelet count of