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[Intervention Review]

Interventions for preventing reactions to snake antivenom

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ABSTRACT

Background

Antivenom is used to neutralise snake bite toxins in people showing evidence of envenomation. It is made from animal sera, and adverse effects, including life threatening anaphylaxis, are common.

Objectives

To assess the effects of drugs given routinely with snake antivenom to prevent adverse effects.

Search methods

Cochrane controlled trials register; contact with researchers in the field.

Selection criteria

Randomized and quasi-randomized trials testing routine adrenaline (epinephrine), antihistamines, or corticosteroids.

Data collection and analysis

The two authors applied the inclusion criteria, assessed trial quality, and extracted the data. We sought additional data from trialists where required.

Main results

One trial in Sri Lanka (n = 105) giving adrenaline with polyspecific antivenom showed fewer adverse reactions in the adrenaline group, and this effect was preserved when stratified for severity. One trial in Brazil (n = 101) using three types of Bothrops antivenom showed no benefit of antihistamine drugs.

Authors' conclusions

Routine prophylactic adrenaline for polyvalent antivenom known to have high adverse event rates seems sensible, based on this one trial. If clinicians believe local factors do not justify routine adrenaline, then they should test their belief in a randomized trial. Antihistamine appears to be of no obvious benefit in preventing acute reactions from antivenoms.

PLAIN LANGUAGE SUMMARY

Interventions for preventing reactions to snake antivenom

People die or can be seriously disabled after being bitten by a venomous snake. Different venomous snake species have different effects on the body, but initial treatment is similar - to try and prevent venom entering the general circulation. If it becomes apparent that the venom has reached the bloodstream, the patients start becoming extremely unwell and in these circumstances health staff may give a specific antivenom (made from horse serum). However, antivenom frequently causes adverse effects which can, in themselves, be severe and result in death.

There are drugs that can be given with the antivenom to try to reduce these adverse effects, and these include adrenaline, antihistamines, and steroids. The review looked to assess the benefit of giving these drugs along with the antivenom. The review of trials found one trial of 105 people in Sri Lanka looking at adrenaline; and a second trial of 101 people in Brazil looking at an antihistamine (promethazine). Both trials were well designed. Adrenaline showed fewer allergic reactions. There was no benefit seen from giving promethazine, and no trials were found on late allergic responses, nor on corticosteroids.

BACKGROUND

There are over 500 species of venomous snakes; only a minority of these bite humans and cause death or disability (Warrell 1995). People with a history of snake bite risk developing symptoms and signs of envenoming, caused by the toxic effects of the venom. Effects vary, depending on the species of snake and dose of venom, but can be fatal.

Incidence and prognosis

There is no overall estimate for the number of snake bites globally, or fatalities. Most figures are unreliable and underestimate the true incidence (Warrell 1995). Rates can be high: for example, one report from northern Ghana estimates an incidence of bites from carpet viper at 86/100,000 of the population each year, with a mortality of 12% (Warrell 1995). In Myanmar, Russell's viper is thought to kill more than 2000 people each year (Warrell 1995).

Aims of treatment

- To reduce the risk of systematic absorption of venom in people bitten by a snake.
- To eliminate the clinical effects of venom.
- To reduce the risk of death in people with evidence of envenoming.

Treatment options for snake envenoming

We categorised the options for treatment into two groups:

Specific measures for bites from particular snakes: This examines treatments by type of snake, and includes (a) specific antivenoms, and (b) specific drugs (such as anticholinesterases for envenoming by cobra).

General measures relevant to all snake bites: This includes first aid measures that aim to reduce systemic absorption, interventions to prevent wound complications, and interventions to prevent reactions to antivenom.

The aim of snake antivenom is to neutralise circulating venom and thus eliminate the toxic effects. This review concerns general measures in preventing reactions to antivenom.

Antivenom is prepared by immunising large animals, usually horses, with a particular snake venom or a range of venoms. Serum from the immunised animal is then processed by salt or caprylic acid and an enzyme, either pepsin or, more recently, papain (Theakston 1997). This is done in one of several specialist laboratories worldwide. The main problem with antivenom is that foreign animal proteins (from the immunised animal) frequently cause reactions, which could be severe and life threatening.

Antivenom reactions can be classified as early and late reactions. Early antivenom reactions may be mild (itch, nausea, vomiting, diarrhoea, headache, or fever), but sometimes severe systemic anaphylaxis develops with bronchospasm, hypotension or angioedema, occurring 10 minutes to 3 hours after exposure to antivenom. These early reactions are not IgE mediated, and are most likely caused by complement activation by IgG aggregates that are in horse serum (Sutherland 1977, Malasit 1986). These early reactions could not be predicted by skin or conjunctival

sensitivity tests (Malasit 1986). These reactions respond readily to subcutaneous adrenaline.

The potential for antivenom to cause anaphylaxis will vary with the particular type of antivenom, the process used to concentrate the antivenom, other aspects of the manufacturing process, and the dose given. The incidence of acute reactions varies from 2-50% of patients. Modification of antivenoms by enzymatic digestion with papain or pepsin, which cleaves IgG, followed by Fc removal can reduce, but not eliminate, acute reactions.

Late (serum sickness type) antivenom reaction can occur 1-2 weeks after treatment with antivenoms. It consists of fever, itching, arthralgia, lymphadenopathy, and albuminuria. The late reaction is caused by immune complex, and responds to treatment with steroids and antihistamines.

To prevent potentially serious adverse effects, different interventions have been used to be given concurrently with antivenom. Adrenaline, antihistamines, and corticosteroids are potential interventions to reduce the incidence and severity of these antivenom reactions. Each of these interventions has a different biological mode of action, and each has different adverse effects:

- Adrenaline (epinephrine) provides immediate physiological reversal of hypersensitivity effects seen in anaphylaxis. It stimulates the cardiovascular system and can cause cardiac arrhythmias.
- Antihistamine drugs are often given with adrenaline, and are thought to prevent anaphylactic relapse. They are relatively safe.
- Corticosteroids are often given in anaphylaxis, and suppress the immune system, but any effect will only become apparent 4-6 hours after the administration of the drug.

Thus adrenaline is the most likely intervention to have an effect in the acute phase, with antihistamines and corticosteroids potentially avoiding relapse or preventing adverse effects of additional doses of antivenom.

All these drugs have some adverse effects, particularly adrenaline, where the adverse effects of the drug itself can be fatal. With adrenaline, this means the balance of benefit over harm when given prophylactically could theoretically vary with the baseline risk of developing the adverse reactions. This risk in turn depends on the quality of the antivenom, and the dose used. These factors therefore need to be taken into account when assessing the generalisability of trials.

The aim of this review is to examine the evidence of benefit and harms when giving adrenaline, antihistamines or corticosteroids routinely with antivenom in patients showing signs of envenoming.

OBJECTIVES

To evaluate drugs given to prevent acute adverse reactions to horse serum antivenom, in relation to anaphylaxis and death.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials.

Types of participants

Patients treated for snake envenoming with horse serum antivenom, irrespective of the snake species.

Types of interventions

1. Adrenaline versus no adrenaline.
2. Steroid versus no steroid.
3. Antihistamine versus no antihistamine.

Trials testing any of the three interventions listed above, where all the patients receive one of the other two interventions, will be included.

Types of outcome measures

Primary

- Death (from any cause).
- Symptoms and signs indicating severe anaphylactic reaction (defined as presence of one or more of the following clinical signs: shock, hypotension, bronchospasm with cyanosis, angioedema, generalised urticaria or gastrointestinal symptoms).

Secondary

- Early (anaphylactoid) reactions: urticaria, angioedema, bronchospasm.
- Late (serum sickness type) reactions: fever, rash, arthritis, lymphadenopathy more than 5 days after antivenom.

Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 1, 2004) and The Cochrane Infectious Diseases Group Specialized Register (March 2004) were searched for relevant trials (published, in press or in progress). The search term used was "snake".

The following databases were also searched: MEDLINE 1966 to March 2004; and EMBASE 1988 to March 2004, using the Cochrane search strategy for identifying trials.

Organisations and individuals working in the field were contacted. These included the Venoms and Toxins Unit, Liverpool School of Tropical Medicine. The external referees were asked to check the completeness of the search strategy, and to identify any additional, ongoing and planned trials.

Data collection and analysis

All identified trials were entered into a trials register. The inclusion criteria were then applied to all possible trials independently by two reviewers. Where they disagreed, a third person was asked for an opinion, and a consensus reached.

All included trials were examined by the two reviewers and each assessed independently the adequacy of concealment of allocation, generation of allocation sequence, inclusion of all randomised patients, and degree of blinding to intervention either observer blind or double blind. We used standard categories for the Cochrane Infectious Diseases Group (see Infectious Diseases Group editorial module in *The Cochrane Library* for details). If the diagnostic criteria for inclusion in studies, the randomisation techniques, the outcome criteria for allergic reactions, or other relevant information were not clearly stated, the authors were contacted for further information.

The following characteristics of included trials were pre-specified as potential sources of heterogeneity, extracted and tabulated: type of snakes; manufacturer of antivenom; and premedication with other drugs before antivenom was given. The pre-specified potential sources of heterogeneity were used to explore possible explanations of variation in effect between trials, and to guide interpretation of the findings.

Differences between the results from individual trials were assessed by visual inspection of the graphs and by a chi-squared test of homogeneity. The presence or absence of heterogeneity was considered before pooling data from more than one trial.

All trials included in this review reported binary outcomes (dichotomous data). The data were entered into Review Manager 5 and each presented as a risk ratio (RR) and a 95% confidence interval (CI).

RESULTS

Description of studies

Two trials met the inclusion criteria (see '[Characteristics of included studies](#)'). One trial was carried out in Sri Lanka in 105 patients to assess adrenaline against a saline control ([Premawardhena 1999](#)). Steroid or antihistamine were not used as premedication. Acute adverse reaction to the antivenom was graded as mild, moderate or severe. Haffkine polyspecific venom was used. The type of snake were Russell's viper (*D. russelli*), cobra (*N. naja*), Sri Lankan krait (*B. ceylonicus*), or uncertain.

The other trial was conducted in 101 Bothrop snake bite patients in Brazil to assess intramuscular promethazine (an antihistamine) against placebo before antivenom was given ([Fan 1999](#)). The patients received one of three types of antivenom, each made by a different manufacturer. The proportion receiving each antivenom was comparable between promethazine and control groups. Adrenaline or steroid was not used as premedication. An acute adverse reaction to the antivenom was graded as mild, moderate or severe.

Risk of bias in included studies

In the adrenaline trial, allocation was adequately concealed as the randomization schedule was known by one of the authors who did not participate in treatment of patients or data collection. Both physicians and patients were blinded. Outcomes were provided in all randomized patients and analysed by intent to treat analysis.

In the antihistamine trial, allocation was adequately concealed in block randomization. Both physicians and patients were blinded.

Outcomes were provided in all randomized patients and analysed by intent to treat analysis.

Effects of interventions

Adrenaline vs placebo

In the adrenaline trial, the group receiving adrenaline suffered fewer adverse allergic reactions overall (adrenalin 6/56; control 21/49; RR 0.25, 95% CI 0.11 to 0.57, [Analysis 1.1](#)). The trend was evident when reactions were stratified by severity: more patients in the placebo group had moderate reactions, while severe reactions occurred in four patients in the placebo group and in none in the adrenaline group (RR 0.10, 95% CI 0.01 to 1.77, [Analysis 1.2](#)). No deaths were recorded.

The investigators also recorded potential adverse effects of adrenaline. No patient developed hypertension (blood pressure >160/100 mmHg), arrhythmia (other than sinus tachycardia), or neurological deficits suggestive of cerebrovascular accidents.

Antihistamines vs placebo

Results from the antihistamine trial showed no difference in acute reactions between the two groups (promethazine 12/49, placebo 13/52; RR 0.98, 95% CI 0.50 to 1.93; [Analysis 2.1](#)). One patient from each treatment group suffered severe anaphylaxis ([Analysis 2.2](#)). No deaths were recorded, and there was no obvious heterogeneity between adverse reactions in the control group and intervention group when stratified by type of antivenom.

DISCUSSION

Both of the studies were well designed. The only study of adrenaline showed the drug had a dramatic effect on adverse acute events, including anaphylaxis, when given prophylactically. Ten per cent (19 of 196) of patients who needed antivenom treatment in this study were not randomized because of medical history of allergy (atopy or wheezing) or cardiovascular risk (age >70 years, hypertension, ischaemic heart disease, or too ill to get consent). Adrenaline at this low dose appears to be safe, but we could not exclude occasional severe adverse effects of the drug as the study size was relatively small.

Antihistamines and steroids are widely used for the purpose of preventing or treating allergic reactions related to horse serum antivenoms, but the one small trial we identified showed no obvious benefit.

Most antivenoms from other manufacturers are horse serum. The use of adrenaline as premedication is likely to prevent acute

reactions similar to those occurring with the antivenom used in this study. Anaphylaxis from antivenom, however, is rare and there is no evidence that adrenaline or any intervention could prevent it.

AUTHORS' CONCLUSIONS

Implications for practice

Clinicians are likely to choose to give adrenaline when the anticipated adverse effects are similar to those for the antivenom used in this trial, at 50%, and the patient has no previous history of cardiovascular risk (hypertension, ischaemic heart disease, transient ischaemic attack, strokes, and age over 70 years). If clinicians consider the antivenom they are using or other conditions are different, and that adrenaline is not justified routinely, then they should be challenged to test their belief in a randomized controlled trial with adrenaline and placebo (see below).

Promethazine is equivalent to placebo, based on one small trial. There is therefore currently no good evidence to give this drug routinely before antivenom.

It has not been assessed whether corticosteroids can prevent adverse effects of horse serum antivenom. They are unlikely to help other than for treating late reactions, or in cases where further doses of antivenom are required some hours after receiving the steroid drug.

Implications for research

With antivenom that is more purified, and associated with fewer adverse effects, it is possible that the balance between benefit and harm of prophylactic adrenaline could be different. In these circumstances, routine adrenaline could be tested in the context of a randomized placebo controlled trial.

It is not known whether the newer generation of antihistamines which block histamine receptors other than H1 receptor would be beneficial in preventing horse serum antivenoms. There is still need for controlled trials to assess whether these newer antihistamines or steroids can prevent adverse effects from horse serum antivenoms in combination with adrenaline.

No trials have been found so far that report on late allergic responses, or the potential role of corticosteroids.

ACKNOWLEDGEMENTS

We thank D Lalloo, RDG Theakston and DA Warrell for their guidance and comments.

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Fan 1999 *{published data only}*

Fan HW, Marcopito LF, Cardoso JLC, Frana FOS, Malaque CMS, Ferrari RA, et al. Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. *BMJ* 1999;**318**:1451-2.

Premawardhena 1999 *{published data only}*

Premawardhena AP, de Silva CE, Fonseka MMD, Gunatilake SB, de Silva JH. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *BMJ* 1999;**318**:1041-3.

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Warrell 1995

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fan 1999

Methods	Randomized, double blind, placebo-controlled study Block randomization was used
Participants	101 Bothrop snake bite patients (adult and children age > 2 years)
Interventions	Antihistamine: 25 mg promethazine as premedication before antivenom Controls: placebo injection
Outcomes	Deaths, severe moderate or mild reactions
Notes	Brazil Three different sources of Bothrop antivenom were used in an unrandomized, uncontrolled fashion Manufacturers: Instituto Butantan, Fundalo ezequiel Dias, or instituto Vital Brazil

Premawardhena 1999

Methods	Randomized controlled trial Randomization by computer generated number
Participants	Adult patients with evidence of systemic envenoming or severe local reaction, given antivenom, 196 eligible, 91 excluded (72 because treatment started in another hospital); 105 randomized
Interventions	Intervention: 0.25 ml of adrenaline subcutaneously Controls: 0.25 ml normal saline subcutaneously

Interventions for preventing reactions to snake antivenom (Review)

Premawardhena 1999 (Continued)

All received 200 ml polyspecific antivenom IV

Outcomes	Deaths, severe moderate or mild reactions
Notes	Sri Lanka
	Manufacturer: Haffkine Lab, India
	Type of snake not specified
	No antihistamines or steroids given

DATA AND ANALYSES

Comparison 1. Adrenaline vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergic reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Severe anaphylaxis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Adrenaline vs placebo, Outcome 1 Any allergic reactions.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Premawardhena 1999	6/56	21/49		0.25[0.11,0.57]
			Favours Treatment	Favours Control

Analysis 1.2. Comparison 1 Adrenaline vs placebo, Outcome 2 Severe anaphylaxis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Premawardhena 1999	0/56	4/49		0.1[0.01,1.77]
			Favours Treatment	Favours Control

Comparison 2. Antihistamines vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergic reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Severe anaphylaxis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Antihistamines vs placebo, Outcome 1 Any allergic reactions.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fan 1999	12/49	13/52		0.98[0.5,1.93]
			Favours Treatment	Favours Control

Analysis 2.2. Comparison 2 Antihistamines vs placebo, Outcome 2 Severe anaphylaxis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fan 1999	1/49	1/52		1.06[0.07,16.5]
			Favours Treatment	Favours Control

WHAT'S NEW

Date	Event	Description
18 August 2008	Amended	Converted to new review format with minor editing.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 2, 2000

Date	Event	Description
24 January 2007	Amended	Plain language summary added to review.
13 November 2006	Amended	Minor update
29 March 2004	Amended	New studies found but not yet included or excluded

CONTRIBUTIONS OF AUTHORS

IN identified the topic, explored the scope of trials in this area, described the trials, co-drafted the protocol, designed the data extraction forms, extracted the data, and drafted the review. PG identified the topics list for this health problem, co-wrote the protocol and review, and advised on methods.

A panel of topic experts advised on this review. David Theakston commented on early documents describing the scope of the literature on this topic, commented on the review, and has provided technical support throughout. David Lalloo (Liverpool) and David Warrell (Oxford) commented on the review.

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Chulalongkorn University, Thailand.
- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (UK), UK.
- European Commission (Directorate General XII), Belgium.
- Health System Research Institute, Thailand.

INDEX TERMS

Medical Subject Headings (MeSH)

*Snake Venoms; Antivenins [*adverse effects]; Drug Hypersensitivity [*etiology] [*prevention & control]; Epinephrine [*therapeutic use]; Glucocorticoids [*therapeutic use]; Histamine H1 Antagonists [*therapeutic use]

MeSH check words

Humans