

Should subcutaneous adrenaline, hydrocortisone or antihistamines be used as premedication for snake antivenom?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *Should s/c adrenaline, hydrocortisone or antihistamines be used as premedication for snake antivenom?*

The WHO Pocketbook of Hospital Care for Children, in Chapter 1.6 on p31, recommends that in the event antivenom is given for snakebite then IM epinephrine and IV chlorpheniramine should be prepared in case allergic reaction occurs.

INTRODUCTION

Managing snake envenomation is challenging throughout the world. Even though antivenom is highly effective in reducing serious complications and mortality^{1,2}, its potential for severe anaphylactoid reactions calls for judicious use³⁻⁵. The frequency of acute reactions to antivenom varies between 2-54%^{6,7} and are responsive to administration of adrenaline^{4-6,8}. The late serum sickness-like reactions can occur in more than 50% of patients^{4,9} and are readily treated with steroids and antihistamines⁵.

These hypersensitivity reactions are mainly caused by the foreign animal proteins present in the antivenom and the probability of a reaction depends partly on the type of antivenom,¹⁰ its manufacturing and concentrating process, and the dose used.^{6,9} Therefore, studies vary in reported hypersensitivity reaction rates due to different antivenoms used and the quality of the antivenom^{7,11,12}. In setting where antivenom reaction rates are high, pre-medication to reduce serious reactions seems a sound approach.

Adrenaline, steroids or antihistamines have been used as pre-medication, with varying results. This review investigates the evidence for the effectiveness of such premedications and intends to answer the question: Should s/c adrenaline, hydrocortisone or antihistamines be used as premedication for snake antivenom?

METHODOLOGY

The clinical search strategy was (antivenins OR antivenom OR snakebite OR snakebite prophylaxis) AND (hydrocortisone OR steroids OR antihistamines OR adrenaline). Clinical filters used were "therapy" and "broad". 126 articles were found. Using the same search term but restricting to systematic reviews, only one relevant article was found.

Of the 126 articles, 66 articles were selected using titles. Of them, 27 were excluded because there were no abstracts and were published prior to 1980 (13) or because the articles were commentaries or letters (14). A further 23 articles were excluded after examining the abstracts, as they were not relevant to the question. An additional 12 case-series or case-control studies were excluded, leaving one systematic review and three RCTs.

All trials were appraised individually by this review. The systematic review (included two out of the three RCTs) was type 1a and the three RCTs were type 1b evidence (Oxford grading system).

RESULTS

Subcutaneous adrenaline

An RCT (n=105) using 0.25ml 1 in 1000 adrenaline showed significant reduction in acute adverse reactions between the adrenaline group (6/56) and the placebo group (21/49) with a relative risk of 0.25 (P value of 0.0002, 95%CI = 0.11 - 0.57). The differences consistently applied to each category of mild (P=0.05, 95%CI = 0.05 to 1.15), moderate (P=0.04, 95%CI = 0.12 to 1.05) and severe reactions (p=0.04, 95%CI = 0.00 to 1.13)¹³. No severe adverse effects were attributed to adrenaline use.

Hydrocortisone

There is no large RCT using hydrocortisone alone as premedication for snake antivenom treatment. However, in one small RCT, adverse reactions were observed in 80% (12/15) of the treatment group (hydrocortisone only) and 81% (13/16) of the placebo group. One percentage point reduction, 95% CI = -29% to 27%. The author concluded that "prophylaxis with a parallel hydrocortisone infusion alone is ineffective in reducing the occurrence of acute adverse reaction to antivenom serum"¹⁴.

Antihistamines

In one RCT (n=101) promethazine (H1 antagonist) was used as pre-medication. Early anaphylactic reactions occurred in 12/49 of the treatment group and 13/52 of the placebo group¹⁵. RR = 0.98, 95%CI = 0.50 to 1.93⁶. The study demonstrated that premedication (15-20 min prior to antivenom administration) with intramuscular promethazine was ineffective in preventing early anaphylactic reactions.¹⁵

A smaller RCT showed that combination of hydrocortisone infusion and intravenous bolus chlorpheniramine (H1 antagonist) could significantly reduce the incidence of adverse reactions compared to placebo. 52%(11/21) in combined hydrocortisone and chlorpheniramine group and 81%(13/16) in placebo group. 29% reduction, 95% CI = 0.2%-58%, P = 0.04.¹⁴ However, its statistical significance has been questioned by at least two authors.^{16, 17}

DISCUSSION

Subcutaneous adrenaline

Even though subcutaneous adrenaline appears to be a potent premedication in reducing acute adverse reactions when given prophylactically, the single trial showing its effectiveness had strict exclusion criteria. In particular, patients below 12 years old were not enrolled¹³. Therefore, the use of s/c adrenaline in children has not been proven and a decision on appropriate dosing and consultation with an experienced clinician would be necessary prior to pre-treatment with adrenaline. In addition, in areas where antivenom adverse reactions rates are low, the benefit of adrenaline needs to weigh against its potential risks. A local study might be needed for such justification⁶.

Hydrocortisone

Despite its common use as a prophylaxis against acute adverse reactions of snake antivenoms¹⁴, there is no evidence behind such practice. Instead, it was suggested that hydrocortisone is unlikely to help preventing acute adverse reactions.^{6,14} However, there is no large RCT to refute such claims. The potential benefit of prophylactic hydrocortisone in reducing relapses of acute reactions and incidence of late reaction are yet to be determined.^{6,14} Nevertheless, it is commonly accepted that hydrocortisone be used to treat late reactions.^{5, 6, 18}

Antihistamines

Previous studies indicated antihistamines are ineffective in preventing acute adverse reactions^{6, 15}. A recent underpowered study proposed a synergistic effect of hydrocortisone and antihistamines that might have led to the different results¹⁴. Therefore, further studies are needed to examine the proposal and to justify the benefits of such combination therapy against its potential side-effects.

SUMMARY

Premedication with subcutaneous adrenaline is effective in reducing acute adverse reactions due to snake antivenom (Grade A recommendation). However, local factors and patient selection need to be considered carefully. There is no strong evidence to support the use of hydrocortisone as premedication

for snake antivenom (Grade B recommendation). Current evidence does not support routine antihistamines use as premedication for snake antivenom (Grade A recommendation). Further studies are needed to verify effectiveness of combination therapy with hydrocortisone and antihistamines. Doses of sub-cutaneous adrenaline as pre-medication for younger children are yet to be evaluated in clinical trials, but fractional doses based on weight may be appropriate.

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