Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites

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Abstract

Objective To investigate the efficacy of the H_1 antihistamine promethazine against early anaphylactic reactions to antivenom.
Design Sequential randomised, double blind, placebo controlled trial.
Setting Public hospital in a venom research institute, São Paulo, Brazil.
Participants 101 patients requiring antivenom treatment after being bitten by bothrops snakes.
Intervention Intramuscular injection of promethazine (25 mg for adults and 0.5/kg for children) or placebo given 15-20 min before starting intravenous infusion of antivenom.
Main outcome measures Incidence and severity of anaphylactic reactions occurring within 24 hours after antivenom.
Results Reactions occurred in 12 of 49 patients treated with promethazine (24%) and in 13 of 52 given placebo (25%); most were mild or moderate. Continuous sequential analysis indicated that the study could be interrupted at the 22nd untied pair, without preference for promethazine or placebo.
Conclusion Prophylaxis with promethazine does not prevent early reactions. Patients should be observed carefully during antivenom infusion and the subsequent few hours.

Introduction

About 20 000 snake bites are reported yearly in Brazil.[1] Antivenom (hyperimmune immunoglobulin), the only specific antidote, may cause anaphylactic or anaphylactoid reactions,[2–5] depending on the type of antivenom, dose, mode of administration, and previous exposure to animal proteins.[6] Adverse reactions cannot be predicted by sensitivity tests,[7] and the reported frequency is as high as 87%.[3] Urticaria, angio-oedema, and gastrointestinal symptoms are the commonest manifestations, but bronchospasm and shock may be fatal.

Prophylaxis with antihistamines (H_1 blockers with or without H_2 blockers) has been proposed.[8–10] However, there have been no properly controlled studies. The aim of this study was to test whether intramuscular promethazine, a widely recommended prophylactic treatment in Brazil[11] and other countries, was effective in preventing early anaphylactic reactions.

Participants and methods

We recruited consecutive patients over 2 years old attending Hospital Vital Brazil, Instituto Butantan, São Paulo, Brazil, after being bitten by bothrops snakes. We excluded patients who had received antihistamine, corticosteroids, or antivenom before reaching hospital, pregnant women, and patients with severe haemorrhage, hypotension, or acute renal failure.[1] Oral informed consent was obtained.

This study was a randomised, double blind, placebo controlled trial followed by sequential analysis. To ensure an equal number of patients in each group and to avoid breaking the code we used block randomisation.[12 13] Identical ampoules were labelled in numerical order and arranged in randomised blocks of six, each block containing three promethazine and three placebo ampoules.

Patients received a deep intramuscular injection of placebo or 25 mg promethazine (2 ml for adults and 0.04 ml/kg (representing 0.5 mg/kg) for children under 50 kg) into the deltoid muscle 15-20 minutes before antivenom therapy. Then, according to clinical severity, either 40 or 80 ml of bothrops antivenom (Instituto Butantan, Fundação Ezequiel Dias, or Instituto Vital Brazil) diluted 1:5 in saline, was given intravenously over about 20 or 40 minutes.

Patients were observed during infusion with antivenom and for 24 hours subsequently. Early reactions were recorded as mild (restricted urticaria, facial flush, dry cough, and hoarseness), moderate (extensive urticaria, nausea, vomiting, abdominal cramps, diarrhoea, and bronchospasm), or severe (glottal oedema, hypotension, and shock).

Statistical analysis

We compared treatments by continuous sequential analysis[14] using the open scheme for explanatory approach.[15] Proportion of success (no reaction) with placebo (p_1) was estimated as 0.70 and that with promethazine (p_2) as 0.875 (25% improvement for promethazine group); type I error (α) = 0.10, type II error (β) = 0.05. A figure was constructed with a horizontal axis representing the number of untied pairs (n), a vertical axis (y) representing excess of preferences for promethazine or placebo, two external boundaries (U and L) limiting preference zones, and two internal boundaries (M and M) limiting the no preference zone.

Pairs consisted of one patient from each group in order of entrance to the study. Only untied pairs (reaction occurring in a patient of one group but not in the other) were taken into account. An arbitrary value of +1 was given for pairs in which preference was for promethazine (no reaction with promethazine and reaction with placebo) and −1 when the preference was for placebo (reaction with promethazine and no reaction with placebo). A diagonal line was drawn in each square of the sequential scheme, and the study was interrupted when one boundary was reached (see *BMJ*'s website for more information).

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Further details of the methods and a figure are available on the BMJ's website

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Table 1 Characteristics of groups before treatment

Variable	Promethazine group (n=49)	Placebo group (n=52)
Sex		
Male	39	41
Female	10	11
Age (years)		
≤14	9	6
>14	40	46
Systemic bleeding		
Yes	7	6
No	42	46
Blood clotting		
Unclottable	19	24
Clottable	30	28
Severity of envenoming		
Mild	36	40
Moderate	13	12
Antivenom		
Instituto Vital Brazil	24	23
Instituto Butantan	19	17
Fundação Ezequiel Dias	6	12
Speed of infusion (ml/min)		
<1.6	25	31
1.6-2.4	23	19
>2.4	1	2

Based on a probability of obtaining an untied pair $\varphi = 0.35$ and finishing the study at the 20th untied pair if there were no preferences, we calculated the sample size as n = minimum number of untied pairs × 2/ probability of obtaining a untied pair, where n = 114.

A database was constructed with Epi-Info 6.0 software. We used the χ^2 test for trend, χ^2 test for determining heterogeneity between proportions, and Student's *t* or non-parametric Kruskall-Wallis tests for comparing means.

Results

Between March 1994 and June 1995 we recruited 101 patients. Twenty three patients were excluded (13 had received antivenom and 10 antihistamine or steroids before admission, nine had no symptoms of envenoming, and two were pregnant.)

Forty nine patients received promethazine and 52 placebo. Both groups were similar at baseline (table 1). Early anaphylactic reactions occurred in 25 of 101 patients. All responded promptly to adrenaline. Three other patients had pyrogenic reactions which were treated symptomatically.

Of the 25 patients who developed reactions, 12 had received prophylactic promethazine and 13 placebo (table 2). There were no differences in the type of antivenom administered (table 3) or the severity of reaction (table 4) between the two groups. Two patients had severe reactions: one developed laryngeal oedema and stridor (promethazine group) and one hypotension (placebo group). Nine patients given promethazine developed reactions during antivenom infusion compared with eight given placebo (P = 0.67). The mean (SD) time after starting the infusion that the reaction occurred was 28.1 (16.2) min for promethazine and 25.0 (19.1) min for placebo (P = 0.66). Anaphylaxis occurred 1-2 hours after the end of antivenom infusion in three patients given promethazine and five given placebo.

Construction of pairs and sequential analysis

There were 22 untied pairs among the 101 patients. A line was plotted showing the sum of the scores for successive pairs. The study was finished when the middle boundary was reached at the 22nd untied pair, indicating no difference between promethazine or placebo (see figure on *BMJ*'s website).

Table 2 Distribution of early anaphylactic reactions according to treatment

Group	No of patients	No (%) with reaction	95% CI (%)
Promethazine	49	12 (24)	13 to 39
Placebo	52	13 (25)	14 to 39
Total	101	25 (25)	17 to 34

Table 3 Early anaphylactic reactions according to the type of antivenom administered

Type of antivenom	Promethazine	Placebo	Total*	P value
Instituto Vital Brazil	6	3	9	
Instituto Butantan	6	5	11	0.432
Fundação Ezequiel Dias	0	5	5	
Total	12	13	25	

*χ^2 for heterogeneity=6.06, P=0.432.

Table 4 Severity and clinical manifestations of early anaphylactic reactions

Severity	Promethazine	Placebo	Total
Mild	8	5	13
Moderate	3	7	10
Severe	1	1	2
Total	12	13	25

χ^2 for trend=1.12, P=0.29.

Discussion

Reactions to antivenom remain common despite improvements in manufacturing processes.[2–7] Prophylaxis is therefore important.[4 8–10] H_1 and H_2 antihistamines, corticosteroids, and adrenaline have been recommended based on anecdotal experience,[9 10 16–19] but no prospective controlled trials have been reported.

We tested intramuscular promethazine because it is routinely used as prophylaxis in many countries. Its efficacy needed to be proved as it can cause complications, such as sedation or anticholinergic effects, that simulate or conceal important symptoms of envenoming. We found that intramuscular promethazine given 15-20 min before the start of bothrops antivenom did not prevent early anaphylactic reactions. This result cannot be attributed to the time of injection as adequate levels of promethazine would have been circulating by the time the antivenom was administered.[20] However, promethazine does not block H_2 receptors, which may be important in anaphylaxis.[21]

Most reactions (68%) occurred during antivenom infusion. Patients should therefore be observed during administration and for at least 2 hours subsequently. Early anaphylactic reactions are promptly reversed by adrenaline.[4]

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Contributors: HWF participated in the formulation of the primary study hypothesis, discussed core ideas, and participated in the protocol design, data collection, analysis, and writing the paper. LFM discussed the core ideas, designed the protocol, and participated in the statistical analysis and interpretation of the data and editing the paper. JLCC initiated the research, discussed core ideas and interpretation of the findings,

participated in data collection, and contributed to the paper. FOSF participated in the design and execution of the study, collected data, and discussed the interpretation of the findings. CMSM initiated the project, discussed ethical issues of the study and its design, collected data, and contributed to the paper. RAF participated in study design, data collection, and interpretation of results and contributed to the paper. RDGT initiated the formulation of the primary study hypothesis, discussed core ideas, and participated in the protocol design, analysis, and interpretation of the data and editing the paper. DAW initiated and coordinated the formulation of the main hypothesis, discussed core issues, participated in the design of the protocol, discussed the interpretation of the findings, and participated in the writing of the paper.

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Key messages

- Antivenom therapy may cause early anaphylactic reactions
- Various drugs are used to prevent reactions, but none have been tested in randomised controlled studies
- This study showed that promethazine is not better than placebo at preventing early reactions
- Although most reactions are mild or moderate, trials of other drugs should be done to reduce frequency of anaphylaxis

The nuclear industry family study: linkage of occupational exposures to reproduction and child health

Noreen Maconochie, Pat Doyle, Eve Roman, Graham Davies, Peter G Smith, Valerie Beral

Concern about high rates of leukaemia and non-Hodgkin's lymphoma among children and young adults living near certain nuclear establishments in the United Kingdom has led to a series of population based case-control studies.[1 2] All these studies have investigated the possibility that the excesses were related to parental employment in those establishments, but the statistical power to detect anything other than extreme associations was very low owing to the rarity of employment in the nuclear industry (coupled with the rarity of the outcome). Moreover, if harmful parental occupational exposures were to exist it is unlikely that their effect would be restricted to cancer among workers' children; such exposures might be expected to influence a broader spectrum of reproductive problems, including infertility, miscarriage, and congenital malformations. These other aspects of reproduction remain largely unexplored.

The nuclear industry family study was set up to examine the occupational histories of a large cohort of nuclear industry workers in relation to all aspects of their reproduction and children's health. A full report of the methods is available on the *BMJ*'s website.

Subjects, methods, and results

The survey population consisted of all employees of the Atomic Energy Authority, the Atomic Weapons Establishment, and British Nuclear Fuels who were in service at the time of the study, between 1993 and 1996 (8100, 6610, and 15 550 workers respectively). Also included were past employees of the Atomic Energy Authority and British Nuclear Fuels who were aged under 75 years and who had an active or preserved pension administered by their joint pensions administration office (9678 and 6458 workers respectively). Of the survey population, 78% was male (36 342 workers).

Postal questionnaires were used to collect details of all reproductive attempts and the health of any children. Questions relating to periods of infertility were also included. Medical outcomes of interest were validated, with appropriate permission, by using clinical notes. Date of conception was estimated as the date of the end of pregnancy, minus gestational age, plus 14 days. Gestation was estimated as 40 weeks for most liveborn children (36 weeks or 28 weeks if

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A full report of the methods of the study is available on the BMJ's website

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