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Research article

Routine prophylactic antibiotic use in the management of snakebite

Dexter D Tagwireyi[1], Douglas E Ball*[1] and Charles FB Nhachi[2]

Address: [1]Drug and Toxicology Information Service, Department of Pharmacy, University of Zimbabwe, Box A178, Avondale, Harare, Zimbabwe and [2]Department of Clinical Pharmacology, Medical School, University of Zimbabwe, Box A178, Avondale, Harare, Zimbabwe

E-mail: Dexter D Tagwireyi - dtagwireyi@healthnet.zw; Douglas E Ball* - dball@healthnet.zw; Charles FB Nhachi - cnhachi@healthnet.zw

*Corresponding author

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Abstract

Background: Routine antibiotic prophylaxis following snakebite is not recommended but evidence suggests that it may be common practice in Zimbabwe. This study set out to determine and describe the extent of this practice at Parirenyatwa Hospital, a large teaching hospital in Zimbabwe

Methods: A retrospective case review (1996 to 1999 inclusive) of all cases of snakebite was undertaken at Parirenyatwa Hospital. Cases with a diagnosis of snakebite, presenting within 24 hours of the bite and with no complications or concurrent illness were defined as "routine prophylactic antibiotic use".

Results: From 78 cases which satisfied the inclusion criteria, 69 (88.5%) received antibiotics. Ten different antibiotics from 6 different classes were used with penicillins the most commonly prescribed (benzylpenicillin in 29% of cases, alone or in combination). Over 40% of antibiotics were given parenterally although all patients were conscious on admission. The total cost of antibiotics used was estimated at US$522.98.

Conclusion: Routine prophylactic use of antibiotics in snakebite at Parirenyatwa Hospital is common practice. This may highlight the lack of a clearly defined policy leading to wasteful inappropriate antibiotic use which is costly and may promote bacterial antibiotic resistance. Further work is required to investigate the reasons for this practice and to design appropriate interventions to counter it.

Background

The routine prophylactic use of antibiotics in the management of snakebite has been advocated and recommended by some authors [1]. This approach has been based largely on sparse and often conflicting evidence concerning the bacterial flora of the oral cavity and venom of snakes [2] and the assumption that a snakebite would result in soft tissue infection at the bite site. The snakebite victim's skin and clothing, materials used for first aid treatment, and the hospital environment have also been implicated as other possible sources of bacterial infection [2]. However, results of studies have failed to show clinical evidence on the benefit of this prophylactic use of antibiotics [3,4] and there is a low incidence of wound infection after snakebite [5]. In view of this, the routine use of antibiotics is generally not advocated and can be considered inappropriate, save for cases of snakebite associated with local tissue necrosis or gangrene

[6,7], abscess formation [8], or bullae [9]. This point has been emphasised by previous authors with regard to snakebite in Zimbabwe [10,11] as well as by our national Drug and Toxicology Information Service (DaTIS) [12]. Studies in Zimbabwe have shown that antibiotics are the most frequently used medication in the management of snakebite [11,13,14] with some authors suggesting that in most instances the use of antibiotics for snakebite was inappropriate and irrational [11,13,15]. However, none of these studies attempted to establish the extent of routine prophylactic use of antibiotics in snakebite since they did not exclude cases where the antibiotics may have been warranted such as necrotising bite areas, coexisting bacterial infections or local complications of snake venom. In view of this and because of the financial implications, we studied routine prophylactic antibiotic use in snakebite at one of the largest referral hospitals in the country in order to assess the extent of this practice and to identify which antibiotics are most commonly used.

Methods

A retrospective review of all case notes (including both physician's and nurse's notes) of snakebite was conducted at Parirenyatwa Hospital, Harare, Zimbabwe for the period January 1996 – December 1999 inclusive. The diagnosis of "snakebite" in all cases was made by emergency department physicians and records were filed whether or not patients were admitted to the hospital. The case notes were traced using the International Classification of Diseases code 989.5[16] for poisoning by snake venom or bite. Inclusion criteria for "routine prophylactic antibiotic use" required that patients presented to the hospital on the day of or the following day to the bite and did not exhibit complications or evidence of necrosis e.g. darkening of the bite site, abscess formation, bullae formation or any other sign of infection which would require antibiotics. If no abnormalities were mentioned in the case notes it was assumed that none were present.

Any patients presenting more than a day after the snakebite were excluded from the analysis since they were assumed to be seeking treatment because of complications and not due to the bite itself and therefore any therapy given could not be defined as routine.

Data was recorded and assessed on a standard data collection sheet by a clinical toxicologist (DT) from the poisons information centre. This data included the date that the bite occurred, date that patient presented to the hospital, antibiotic therapy given on admission and/or in the Emergency Department, the presence of coexisting illnesses and/or injuries and any recorded local signs and symptoms at the bite site. Whilst the hospital computers could select case numbers by ICD-9 code, the laborious nature of locating and browsing records by hand and manpower limitations precluded validation of the data extraction procedure by a second person.

Financial implications

It is the policy of the Pharmacy Department at Parirenyatwa Hospital to supply a full one week course of oral antibiotics to all hospital inpatients for capsules and tablets and a three day course for patients on parenteral antibiotics. For children, a 100 ml suspension is normally supplied. An estimate of cost of antibiotics prescribed for adults was calculated based on the retail cost of the drug (wholesale cost + 50%), the defined daily dose (DDD) for the antibiotic and the hospital pharmacy policy of supplying antibiotics. To estimate the cost of antibiotics prescribed for children (under 12 yrs), it was assumed that the average daily dose was half that of the DDD in adults. For oral doses, the cost of a 100 ml suspension of the antibiotic was used. The costs were calculated using prices as valid on 1st July 2000 and the exchange rate of US$1=Z$38.

Results

A total of 103 cases diagnosed as due to snakebite for the study period were identified. Nineteen cases were excluded (15 on the basis that they had presented two days or more after the bite, in 3 cases the date of snakebite was not recorded and 1 was excluded as the snake had spat into the patient's eyes and not actually bitten them). Therefore a total of 84 patients presented either on the day of the bite or on the following day. Of these, 3 had necrosis and 2 abscess formation at the bite site and were excluded as these symptoms were considered complications warranting antibiotic use and therefore did not warrant "routine prophylactic antibiotic use". Four cases had a coexisting illness (2 hypertensive, 1 peptic ulcer disease on antacid therapy and 1 with a productive cough on no drugs). The patient with the productive cough was excluded as this may have warranted antibiotic use. Details of the excluded patients and the antibiotics they received are shown in Table 1.

In all, 78 cases satisfied the inclusion criteria (Table 2) as potential candidates of routine prophylactic antibiotic use. Sixty-nine (88.5%) received antibiotics (31 male; the sex of one case not recorded). The ages in these cases ranged from 5 to 62 years (n = 68; median 21.5 yr) with 14 cases being below the age of 12 years. All patients were conscious on admission. The length of hospital stay ranged from 1 to 16 days (n = 68; median 2.5 days). Only two patients received antivenin of which one also received an antibiotic (amoxycillin orally). No culture and sensitivity tests were done before instituting the antibiotic therapy in any of the cases and there were no fatalities in the series.

Table 1 : Case details of patients who were excluded from the definition of routine antibiotic use

Age (yrs)	Sex (M/F)	Reason for exclusion	Antibiotics on admission	Length of hospital stay (days)	Antibiotics on discharge
43	M	Darkening of bite site	Benzylpenicillin	4	none
16	M	Darkening of bite site	Benzylpenicillin	4	none
4	M	Darkening of bite site	Amoxycillin	2	none
7	M	Abscess	Benzylpenicillin Gentamicin	2	none
58	M	Abscess	Benzyl penicillin Cloxacillin Metronidazole	6	none
48	M	Productive cough	Ampicillin	2	Amoxycillin

Table 2 : Local clinical signs and symptoms of all study cases of suspected snakebite

Local clinical signs and symptoms	Cases presenting (n = 78)	Cases receiving antibiotics (n = 69)
Pain with swelling	39	36
Pain with swelling and warmth	14	13
Swelling only	11	9
Pain only	6	6
No signs of snakebite	4	3
Fang marks only	2	1
Pain with swelling and incision*	1	1
Swelling with warmth	1	1

Cuts made by traditional healers in Zimbabwe

Table 3 : Frequency of use of inappropriate routine antibiotics.

Drug	Cases receiving oral antibiotics		Cases receiving parenteral antibiotics		Total
	Adults	Children	Adults	Children	
Benzylpenicillin	0	0	24	7	31
Amoxycillin*	14	6	0	0	20
Cloxacillin	9	3	3	0	15
Ampicillin *	5	2	6	0	13
Metronidazole	10	0	0	1	11
Gentamicin	0	0	3	2	5
Clindamycin	2	0	0	0	2
Chloramphenicol*	4	0	0	0	4
Penicillin V	3	0	0	0	3
Erythromycin*	3	0	0	0	3
Total	**50**	**11**	**36**	**10**	**107**

*Drugs considered as broad spectrum antibiotics

Table 4 : Common antibiotics combinations found in the study.

Antibiotic combination*	No. of cases
benzylpenicillin alone	8
amoxycillin alone	7
benzylpenicillin and metronidazole	5
cloxacillin alone	3
benzylpenicillin and cloxacillin	3
ampicillin alone	2
benzylpenicillin and gentamycin	2

* reflects only those combinations used in 2 or more cases

Antibiotics utilised

A total of 10 different types of antibiotics (from 6 classes namely, penicillins, macrolides, chloramphenicols, aminoglycosides, lincosamides and nitro-imidazoles) were used (Table 3). Penicillins were the most frequently used antibiotics (76.6% of all antibiotics used) with benzylpenicillin being the most widely prescribed (29.0% of all cases) either alone or in combination (Tables 3 and 4). A large proportion of the antibiotics utilised (42.2%) were given parenterally and 37.4% were broad-spectrum antibiotics (Table 3).

The total cost of antibiotics for adult patients was calculated to be Z$3525.84 for oral and Z$12285.07 for parenteral preparations. The cost of antibiotic therapy in paediatric patients was Z$933.36 for oral and Z$3128.69 for parenteral doses. The total cost of antibiotics used was therefore estimated to be Z$19872.96 (US$522.98).

Discussion

Venomous snakes in Zimbabwe fall into four main families namely elapidae (cobras and mambas), colubridae (boomslang), viperidae (adders or vipers) and atractaspididae (asps) and have been extensively described elsewhere in the literature [10,12,14,15]. It is claimed that, of the venomous snakes, cytotoxic adder bites e.g. puff adder (*Bitis* spp.) are the most common, followed by neurotoxic cobra (*Naja* spp.) and mamba (*Dendroasapis* spp.) bites with haemotoxic boomslang (*Dispholidus typus*) bites rarely seen[13], a large number of non-venomous snakes also abound which may be responsible for bites. The incidence of non-venomous bites and/or "dry" bites by venomous snakes is taken to be high in the catchment area of Parirenyatwa Hospital, an assumption supported by the fact that only two cases received antivenin in this series. Despite the availability of information on dangerous snakes in Zimbabwe, those responsible for the greater proportion of bites are seldom identified by health care professionals. This can be attributed to the fact that most bites occur in the night when visibility is low. In addition, even if the culprit snake is seen, patients presenting to health facilities are seldom able to identify it, and rarely bring dead snakes along with them. Treatment of snakebite at health care facilities in Zimbabwe is therefore nearly always based on presenting clinical signs and symptoms.

Whilst this study was set out to examine and describe the extent of routine prophylactic antibiotic use in snakebite, it is useful to consider those situations in which antibiotic use is appropriate. Necrosis at the snakebite area provides an ideal setting for the proliferation of microorganisms, a situation which may be worsened by the use of a tourniquet [2,17]. However, bacterial infection is not always present at the necrotised snakebite site as evidenced by the absence of bacterial growth from necrosis due to bites from the Southern African puff adder (*Bitis arietans*) and rhombic nightadder (*Caucus rhombeatus*) [7]. Moreover, cultures of the oral cavities and venoms of different snakes [1,2,18], and swabs from necrotic bite sites and abscesses have shown a wide variety of both aerobic (Gram positive and Gram negative) and anaerobic bacteria including *Clostridium* spp [3,7,8,17,19]. In view of this, antibiotic therapy after necrosis should be based on cultures and antibiotic susceptibility testing, a point which has been stressed by other workers [2,20]. The 3 patients (excluded from the analysis) who presented with necrosis in the present study all received empiric antibiotic therapy and no culture and sensitivity tests were done despite the availability of facilities to carry these tests out at the hospital. It has been suggested that if antibiotics are to be used prophylactically for snakebite in Southern Africa, then Gram-negative aerobic *Enterobacteriaceae* and *Staphylococcus* spp. must be covered [7]. However since the range of bacteria from the venom and oral cavities of snakes vary with geographic area, the species and oral health of the snake [21], this cannot be easily extrapolated to snakes in Zimbabwe. Moreover, the "blind" use of antibiotics covering such a broad spectrum of activity may promote the emergence of antibacterial drug resistance.

Bacteria are a major cause of abscess formation but the role of prophylactic antibiotics to prevent their formation is questionable [22]. Proteolytic effects of some snake venoms may cause local reactions that also have a role to play in the pathogenesis of abscess formation [8]. The two patients (excluded) who presented with abscess formation both received antibiotics. The use of antibiotics may prevent dissemination of the infection and accelerate healing [8]. However, as in the case of suspected infection of necrotic areas and for the same reasons, it is desirable to perform culture and sensitivity tests before commencing antibiotic therapy.

There is little clinical evidence of the benefit of prophylactic antibiotics after snakebite [3–5] and the routine use of antibiotics is not advocated except for cases of snakebite associated with complications or signs of infection [6–9]. In the present study, well over three quarters of patients received routine prophylactic antibiotic therapy (88.5%). The reason for this may be attributed to genuine concern over the occurrence of tissue infection after snakebite even where no local complications due to the venom or otherwise are present. However, it is also possible that antibiotics are given to patients simply as a form of reassurance to make the patients believe that they were receiving proper treatment. The relatively large proportion of patients (42.2%) who received parenteral antibiotics despite all patients being conscious on admission may support this speculation since injections may be viewed as superior treatment than oral medicines in some cultures [23]. The fact that both patients who received antivenin did not receive parenteral preparations suggests this may be an important consideration. The use of antibiotics for the purposes of prophylaxis against infection accounts for most misuse of these drugs. Zimbabwe is a developing country with limited medical and financial resources, and rational use of drugs is promoted in the National Drug Policy [24] in order to better manage these resources. Routine prophylactic antibiotic use for snakebite should therefore be limited only to cases where they are truly needed as documented in the literature [4,7–9]. Using antibiotics routinely for snakebite is not cost effective and puts undue financial pressure on patients who have to pay for antibiotics they do not really need. This is more so with the routine use of parenteral antibiotics which are generally more costly (exemplified by our results) and carry risks inherent to invasive procedures. In this study, we estimated the total cost of the drugs to the patient to be US$522. This is an underestimate of the actual costs of antibiotic therapy as it excludes syringes, needles, health worker time and similar costs and ignores devaluation and depreciation of the Zimbabwe dollar between 1996 and 2000. Moreover, the emergence of antibiotic resistance is primarily due to excessive and often unnecessary use of antibiotics in humans and animals[25], high routine prophylactic use of antibiotics in snakebite as demonstrated in this study may therefore lead to antibiotic resistance with implications on the use of these drugs in conditions where they are truly needed. Although the number of cases in this series was relatively small and may not impact significantly on antibiotic resistance in itself, when looking at the problem from a national view point and taking into consideration hospitals at lower levels of care e.g. district hospitals, this may still be an relevant concern.

The wide variety of antibiotics used routinely at the study hospital is also of concern. A previous retrospective study at six referral hospitals also demonstrated that an array of antibiotics were used in the management of snakebite in Zimbabwe [13]. Studies from other regions of the world do not appear to follow the same pattern. These include the Asir region of Saudi Arabia and Eastern Ecuador for instance where only ampicillin alone or in combination with another antibiotic were used for snakebite[3,26] This variety in antibiotic prescribing for snakebite in Zimbabwe indicates the lack of a clearly defined policy with regards to this issue. Taken together with the high use of broad spectrum antibiotics (especially amoxycillin and ampicillin), it also demonstrates a lack of knowledge with regards to which pathogenic bacteria exist in the oral cavities of snakes in the region and in what instances infection is most likely to occur. Overuse of broad spectrum antibiotics especially where they are really not required is irrational and has been cited as a major reason for the growing world-wide resistance of bacteria to antibiotics. [27] Whilst a large number of broad spectrum antibiotics were used, it is interesting to note that benzylpenicillin alone was the most widely used antibiotic at the study hospital, something which has been reported at other referral hospitals in Zimbabwe [4,28]. It is possible that the antibiotic is preferred due to its parenteral route of administration and relative safety as compared to other injectable antibiotics. It is also possible that this narrow spectrum antibiotic was favoured by some prescribers because of concern about promoting drug resistance by using broad spectrum agents.

The definition of "routine prophylactic antibiotic use" in the present study was based mainly on retrospective assessment of recorded local clinical signs and symptoms, a methodology which has inherent weaknesses. Since health workers at the time were not aware of the study, records may be incomplete with some observations not being included in patient notes. Thus there may have been omission of important local clinical signs from the records and if no abnormalities were recorded it was assumed there were none. Furthermore, swelling, regardless of severity, was not considered as one of the local clinical signs warranting the use of antibiotics and could have excluded true bacterial cellulitis without sepsis. However, this bias was reduced by excluding all cases presenting more than a day after the snakebite. Excluding patients presenting a day after the bite may have further reduced this bias, but this would have resulted in us missing bites which occurred in the night and where the patient presented to the hospital the next morning – most snakebites are reported to occur in the later hours of the day in Zimbabwe [4,11]. Pyrexia, was also not considered as one of the clinical presentations warranting the use of antibiotics. This was in view of the fact that despite reports of bacteria in snake venom[2] which would lead to systemic infection, it is in fact sterile like other body fluids [9,18]. Some authors have even suggested that some snake venoms may possess antibacterial properties [7,29]. Pyrexia after snakebite is said to be rarely due to sepsis [15] and is more likely to be a consequence of the venom itself rather than systemic infection. However, by excluding fever, we may have missed some infections. Each of these limitations alone or in combination could lead to over-estimation of prophylactic antibiotic use since there may have been additional cases which required antibiotics. However, they are unlikely to explain the high antibiotic prescribing observed.

There may also have been misclassification of records i.e. some cases of snakebite not being filed under the relevant ICD-9 code which was used to locate the case notes. Ideally, the extraction procedure could have been validated by browsing all patient records over a set time period to observe that all snakebite cases were filed appropriately. However, the hospital computer system does not offer simple search and browse methods – once a record number is identified it has to be located physically and browsed by hand. The logistics of this and limitations in manpower made validation unrealistic. However, even if some cases of routine antibiotic prophylaxis in snakebite were missed, this does not reduce the importance of the findings.

Conclusions

Routine prophylactic use of antibiotics in the management of snakebite is common at Parirenyatwa Hospital. This is probably as a consequence of the lack of a clearly defined policy with regards to the exact role of antibiotics in the management of snakebite in Zimbabwe. This practice may lead to wastage of medical resources and put undue financial pressure on the patient who has to purchase unnecessary drugs. This is especially pertinent in developing countries such as Zimbabwe. Furthermore, culture and sensitivity tests should be performed before commencing therapy since bacterial flora in snakes vary greatly, there are chances that necrotic areas may not get infected, and the antibiotics are not being used in life-saving situations. This will reduce overuse of these drugs with implications for the emergence of bacterial drug resistance and adverse reactions in patients. Educational and/or managerial interventions are required to address this situation, but these will need to be complemented by an assessment of the motivations underlying the prescribing habits observed. We trust that this work will also serve as the basis for follow up studies investigating the impact of guidelines on the use of antibiotics in snakebite and to prospective studies of the effect of antibiotics on infection following snakebite.

Competing interests

None declared.

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