

## Clinical safety of a polyvalent F(ab')<sub>2</sub> equine antivenom in 223 African snake envenomations: a field trial in Cameroon

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### Abstract

A large-scale clinical trial was conducted, according to World Health Organization Good Clinical Practice guidelines, in 7 centres in north Cameroon to determine the safety and efficacy of a polyvalent antivenom composed of purified F(ab')<sub>2</sub>. This study included 223 patients presenting clinically with obvious snake bite, predominantly due to *Echis ocellatus* (viper), the most abundant species in this savannah region. Clinical surveillance was maintained for 5 d in all patients and until the twenty-sixth day in 74% of cases. Two 10 mL ampoules of polyvalent F(ab')<sub>2</sub> equine antivenom (Ipser Africa™) were administered to each patient by intravenous infusion. If necessary, treatment was repeated 1 h after the end of the first infusion, and then with a frequency determined by the patient's clinical condition. Before initiation of antivenom treatment, the main clinical disorders observed on admission were oedema (93.7%) and haemorrhage (48.9%), with a clotting time longer than 30 min in 65.4% of patients. Clinical cure was obtained in 213 patients (96.8%). No amputation was necessary, and the case fatality rate was only 1.3%. On average, 4.6 (±3.7) ampoules were administered per patient; 43% of subjects recovered after only a single infusion of 2 ampoules. Early adverse reactions, of varying degrees of severity, were observed in 6.3% of patients. A severe early reaction, anaphylactic shock, was observed in only one patient (0.4%). Serum sickness was observed in another patient. Polyvalent F(ab')<sub>2</sub> equine antivenom given by repeated 20 mL intravenous infusions is a safe and effective treatment for envenomation caused by African vipers.

**Keywords:** snake bite, *Echis ocellatus*, antivenom, Cameroon

### Introduction

Snake bites constitute a serious public health problem in Africa because of their frequency and severity, and also because of the difficulties encountered in their therapeutic management (WARRELL & ARNETT, 1976). The annual number of envenomations in sub-Saharan Africa probably exceeds one million, and the mortality rate can be as high as 28% (CHIPPAUX *et al.*, 1981). Various authors have estimated that in Africa snake bites result in 25 000 to 50 000 deaths per year (PUGH & THEAKSTON, 1980; CHIPPAUX *et al.*, 1996).

Equine antivenoms were developed at the end of the 19th century. Although they are generally considered to be the only effective treatment against envenomation, their use remains controversial. A recent survey indicated that, on the basis of one ampoule per snake bite victim, the current distribution of antivenom in Africa represents less than one-quarter of the needs (CHIPPAUX *et al.*, 1996). This observation can be explained by 3 factors: (i) the fear of early or late intolerance reactions; (ii) the limited availability of antivenom, especially in the bush, which is partly related to the cost of the product; and (iii) ignorance concerning the method of administration and the efficacy of antivenom.

We conducted a large-scale clinical trial in northern Cameroon that had the primary objective of evaluating the early and late reactivity of an intravenously administered polyvalent F(ab')<sub>2</sub> equine antivenom that is available on the African market. The need for such prospective surveys has been emphasized by the World Health Organization (WHO, 1981). The secondary objectives of this field trial were, first, to assess the efficacy of the antivenom, and, second, to outline treatment surveillance indicators appropriate to sub-Saharan Africa. Taking into account the life-threatening nature of African viper envenomation and the established efficacy of equine antivenom (REID & THEAKSTON, 1983; PUGH & THEAKSTON, 1987; CARDOSO *et al.*, 1993; WARRELL, 1996), no placebo group was used.

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### Patients and Methods

#### Study region

Seven health centres in north Cameroon [3 hospitals (Garoua, Touboro, and Tokombéré) and 4 rural dispensaries (Fignolé, Dingiré, Lara and Doukoula)] were selected for participation in this study, based on the high incidence of snake bites in these regions. The study was conducted from 1993 to 1995 in the geographical region of the Sudanese savannah, essentially inhabited by *Echis ocellatus*, a member of the Viperidae possessing a procoagulant venom rich in prothrombin and factor X activators (WARRELL & ARNETT, 1976; YAMADA *et al.*, 1997).

#### Procedures and ethical considerations

This study was conducted in accordance with WHO Good Clinical Practice (GCP) guidelines and the latest revision of the Declaration of Helsinki. The clinical protocol was approved by both the National Ethics Committee and the Cameroon Ministry of Health. After obtaining written informed consent, patients who met inclusion criteria were enrolled in the study. The informed consent form was written in French, but nurses or investigators translated and explained it to the patient in the local language. Clinical data were reported on standardized case report forms (CRFs) by the investigators and were checked regularly during visits by independent study monitors. Statistical analyses were performed after the database was locked.

#### Patients

Patients were included in the study on the basis of set criteria: they had to (i) have been bitten by a snake, (ii) present at least one clinical or laboratory sign of envenomation (i.e., oedema, necrosis, external bleeding, or a whole-blood clotting test time longer than 30 min), (iii) have no known history of intolerance to equine serum, and (iv) provide written informed consent. Patients who had a known history of intolerance to equine serum or only a mild envenomation were not included and received first adrenaline before treatment with Ipser Africa™ if necessary (REID & THEAKSTON, 1983).

#### Treatment

Two commercial batches of polyvalent F(ab')<sub>2</sub> equine antivenom (Ipser Africa™; S2918 and S2924;



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Pasteur Mérieux Connaught, Lyon, France) were used. This antivenom is obtained by immunization of horses with venoms from *Bitis arietans*, *B. gabonica*, *Echis leucogaster*, *Naja melanoleuca*, *N. haje*, *N. nigricollis*, *Dendroaspis viridis*, *D. jamesoni* and *D. augusticeps*. According to a 50% lethal dose (LD<sub>50</sub>) assay in mice (ANONYMOUS, 1997), 1 mL of antivenom neutralizes at least 25 LD<sub>50</sub> of each of these venoms except for those of *N. melanoleuca* and *N. nigricollis*, for which 1 mL of antivenom neutralizes at least 20 LD<sub>50</sub> (ANONYMOUS, 1997). The paraspecificity for *E. ocellatus* is 20 LD<sub>50</sub>/mL. The antivenom is highly purified by ammonium sulphate precipitation of albumin and  $\alpha$ - and  $\beta$ -globulins, fractionation by pepsin to release F(ab)<sub>2</sub> fragments, then dialysis and delipidation by adsorption on aluminium hydroxide. The antivenom is supplied in liquid form in 10 mL ampoules (protein content, 50 mg/mL) and is administered by intravenous infusion.

#### Clinical and biological monitoring

The clinical evaluation of oedema and bleeding was standardized according to MANENT *et al.*, 1992 (Table 1). Microscopical haematuria or proteinuria was identified with reagent dipsticks, and the 30 min whole blood clotting time (WBCT) test was performed in a dry tube. The test was modified from the original method described by WARRELL *et al.* (1977) by lengthening the observation time from 20 min to 30 min. This delay was necessary to perform a clinical examination and to inform the patient of the study before obtaining written consent.

**Table 1. Clinical classification of oedema and bleeding following snake bite<sup>a</sup>**

Score	Oedema	Bleeding
1	Not extending beyond the joint contiguous to the bite	Localized to the bite and persisting >1 h
2	Involving 2 adjacent joints	Involving mucous membranes
3	Extending beyond 2 joints without involving the proximal part of the limb	Involving skin
4	Involving the proximal part of the limb	Visceral haemorrhages (haemoptysis, haematemesis, melaena)
5	Extending beyond the proximal part of the limb	Not applicable

<sup>a</sup>From MANENT *et al.* (1992).

#### Study protocol

Whenever possible, the snake responsible for the envenomation was preserved in alcohol and then formally identified by a herpetologist (J.-P. Chippaux).

After clinical examination and obtaining written consent, the patient was included in the study. Two ampoules, i.e., 20 mL of F(ab)<sub>2</sub> antivenom, were diluted in 250 mL of isotonic glucose solution and administered intravenously over 1 h under constant medical surveillance. Patients were monitored for up to 1 h after the end of the infusion, when another clinical and laboratory assessment was performed under the same conditions as the admission examination. After a further period of 2 h, if necessary, a second infusion was administered under similar conditions to the first (i.e., 1 h infusion, followed by 1 h monitoring period). After the second infusion, in the event of no improvement according to clinical (i.e., persistence of bleedings) or laboratory (i.e., WBCT > 30 min) criteria after a further four-hours observation period, a third antivenom infusion could be administered. Any subsequent infusions were given, if required, at intervals of 6 h. The minimal duration of hospital surveillance defined in the protocol was 5 d, regardless of the severity of the snake bite. Clinical examinations were done at least twice daily until the fifth day. The patient was reviewed in the fourth week after the first administration of antivenom (day 26) to provide a comprehensive evaluation of any late adverse reactions (i.e., serum sickness).

#### Evaluation of safety and efficacy

Safety was evaluated on clinical criteria. All events occurring after treatment were recorded on standardized CRFs. The events were described in terms of their onset (immediate—during the infusion or the ensuing 30 min, early—until day 5, and late—between days 5 and 26), severity (mild, moderate, severe), and relationship to the treatment (doubtful, possible, probable). The development of proteinuria while in hospital or a significant increase in proteinuria after treatment was monitored in order to distinguish renal impairment due to envenomation or intolerance to equine serum from pre-existing bacterial or parasitic infections. As an indicator of late intolerance, we tried to estimate the prevalence of serum sickness, for which the case definition was a combination of fever, arthralgia or myalgia, and pruritus or a rash occurring after day 6 following the first dose of antivenom.

Blood coagulability was considered to be restored when no bleeding was observed (defined as stage 0) and the WBCT was less than 30 min for 2 consecutive days, irrespective of any oedema that might have persisted for several days after blood coagulability restoration, or possible sequelae during healing. The time of patient blood coagulability restoration was retrospectively taken to be the first examination upon which these 2 criteria were satisfied. Examinations were performed every 6 h during treatment and twice a day after the last administration of antivenom.

#### Statistical methods

The statistical methods used were descriptive. Evaluation of defined criteria between inclusion and the successive examinations (days 0, 1, 5 and 26) was performed by Wilcoxon's signed rank test and McNemar's test. Spearman's rank-order correlation and the  $\chi^2$  test, or Fisher's exact test for small sample sizes, were used to determine the relationship between parameters. Statistical analysis used SAS® software (version 6.06 for OS/2; SAS Institute, Inc., Cary, NC, USA). Results are expressed as means  $\pm$  SE.

#### Results

##### Subjects

Between December 1993 and December 1994, 223 patients suffering from snake bite who satisfied the inclusion criteria were included in the study. The majority of patients (97.0%) were recruited at 5 centres (Garoua, Dingtiré, Touboro, Lara, and Doukoula). Almost 60% of patients arrived at the health centre less than 4 h after the bite, and approximately 20% arrived more than 10 h after the bite (Figure). Demographic data for the patient population were as follows: age, 25 ( $\pm$ 1) years; weight, 49 ( $\pm$ 1) kg; height, 158 ( $\pm$ 2) cm. The male/female ratio was 3:2. Children younger than 15 years old represented 34% of the study population, and 4% of the patients were less than 5 years of age.

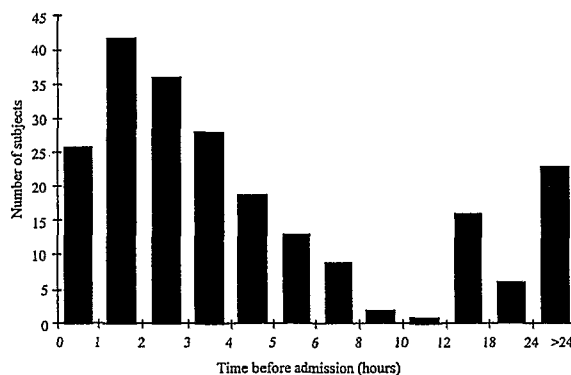


Figure. Interval between snake bite and arrival at the health centre.

The snake responsible for the envenomation was identified by the herpetologist in 59% of cases. *E. ocellatus* represented 55 of the 64 formally identified snakes (86%). Other incriminated species included *Atractaspis microlepidota* (5 cases with formal identification of snake), which are solenoglyph snakes with a necrotic, cardiotoxic, and slightly haemorrhagic venom. *N. haje* and *Causus maculatus* were each incriminated only once (preserved snake was identified), and *B. arietans* was incriminated 6 times (2 from preserved snakes and 4 from a picture). These 6 envenomations were characterized by the need to give larger doses of antivenom; however, no envenomation led to sequelae such as necrosis (WARRELL *et al.*, 1977; PUGH & THEAKSTON, 1987). Most of the other snakes that were not formally identified were probably *E. ocellatus* because of its prevalence, the patient's description of the snake, and the clinical signs observed.

Of the 223 patients included in the study, 205 (91.9%) were examined on day 5 and 164 (73.5%) patients were seen on day 26. The remaining 59 patients left the health centre against medical advice.

#### Clinical examination and severity of envenomation on admission

Oedema was observed in 209 patients (93.7%) on admission. Most patients [133 (59.6%)] presented with stage 1 oedema. Stage 2 oedema was observed in 49 patients (21.9%), stage 3 in 22 patients (9.8%) and stage

**Table 2. Frequency and severity of the 18 immediate (during the first infusion or within the following 30 min) and the 37 early adverse events (onset before day 5 following the first infusion) reported in 20 patients (9%) suffering from snake envenomation**

Events	Immediate adverse events		Early adverse events		Total
	Non-severe <sup>a</sup>	Severe	Non-severe <sup>a</sup>	Severe	
Pruritus	4	1	9	0	14
Vomiting	2	0	7	1	10
Nausea	1	0	3	0	4
Fever	1	0	2	0	3
Hypotension	0	0	2	1	3
Quincke's type oedema	1	1	0	0	2
Generalized urticaria	1	1	0	0	2
Cough	0	0	2	0	2
Abdominal pain	0	0	2	0	2
Dizziness	0	0	2	0	2
Dyspnoea	0	0	0	1	1
Shock	0	0	0	1	1
Headache	0	0	1	0	1
Restlessness	0	0	1	0	1
Others	5	0	2	0	7
Total	15 (27.2%)	3 (5.5%)	33 (60%)	4 (7.3%)	55 (100%)

<sup>a</sup>Mild or moderate intensity.

4 in 5 patients (2.2%). No case of stage 5 oedema occurred. The median time before admission increased with the severity of the oedema ( $P=0.0001$ ; Spearman's rank-order correlation test).

Bleeding at inclusion was reported in 109 of the 223 patients (48.9%). Stage 1 bleeding was observed in 66 cases (29.6%), and stages 2-4 in 43 cases (19.3%). In 13 subjects (5.8%), this bleeding corresponded to stage 4. In 40 of the 43 patients with stage 2-4 bleeding, bleeding stopped definitively after treatment. The mean time to recovery ( $\pm$ SE) for all patients was 29.5 ( $\pm$ 34.4) h, and the median time was 18.3 h. The median time before admission increased with the severity of bleeding ( $P=0.0002$ ; Spearman's rank-order correlation test).

Haematuria was observed in 66 of the 208 patients (31.7%) in whom it was investigated. A significant relationship was observed between the presence of patent bleeding (stage 2 or higher) and the presence of microscopical haematuria by reagent dipstick ( $P=0.004$ ,  $\chi^2$  test). Proteinuria was observed in 84 of the 207 patients tested (40.6%).

The WBCT was longer than 30 min in 142 of the 217 patients (65.4%) for whom this test was performed upon arrival at the health centre. Just over one-half (54.4%) of the patients who arrived within 2 h after the bite (68 patients) had a clotting time longer than 30 min. The relation between time before admission and a high clotting time just failed to achieve statistical significance ( $P=0.052$ ,  $\chi^2$  test). The proportion of patients with a clotting time over 30 min increased as the time to admission lengthened, and was almost 80% in patients arriving more than 4 h after the bite.

#### Safety of the antivenom

An average of  $46\pm 37$  mL ( $\sim 2.3$  infusions per patient) of polyvalent F(ab')<sub>2</sub> equine antivenom were administered per patient. In the hospitals, the number of ampoules per patient varied between 6.3 and 7.7 (a mean of  $7.0\pm 4.8$  ampoules per patient for the 3 hospitals), while in the dispensaries the range was from 2.7 to 4.8 ampoules per patient (a mean of  $3.2\pm 1.8$  ampoules per patient for the 4 dispensaries). There was no correlation between the total volume of F(ab')<sub>2</sub> administered and the time to cure ( $P=0.18$ ,  $r=0.26$ , Spearman's rank-order correlation test).

Among the 223 patients included in this study, 51 (22.9%) developed at least one early or late adverse event. Twenty subjects (9%) had at least one early reaction, whatever the causal relationship with the antivenom (doubtful, possible, probable) (Table 2). Eight of

these 20 patients also had an immediate reaction. Of the 166 patients seen after day 5 (including the 2 patients who died after day 5), 38 (22.9%) had developed at least one late adverse event (Table 3). Only one case of serum sickness (0.6%) was observed. No case of serum sickness-like illness was reported.

Five (2.2%) serious or unexpected adverse events were reported during the study, 3 occurred before day 5, and 2 between day 5 and day 26. Only one serious event was judged to be certainly related to the product infusion, this being a case of anaphylactic shock occurring in a patient who had received equine serum once before this antivenom therapy. The patient rapidly recovered after interruption of the infusion. According to clinical findings, the 4 other serious events, i.e., 3 deaths and one miscarriage (2 months of amenorrhoea), were related to the course of the envenomation (MCNALLY & REITZ, 1987; MANENT *et al.*, 1992).

The number of polyvalent F(ab')<sub>2</sub> equine antivenom administrations did not have a significant relationship with the incidence of early adverse events ( $P=0.2$ , Fish-

**Table 3. Frequency and severity of the 54 delayed adverse events (onset between days 5 and 26) reported by 38 patients (23%) suffering from snake envenomation**

Delayed	Non-severe <sup>a</sup>	Severe	Total
<b>Local events</b>			
Injection site oedema	5	0	5
Bite site events	3	0	3
<b>Systemic events</b>			
Fever	8	0	8
Pruritus	0	7	7
Nausea	6	0	6
Arthralgia	5	1	6
Urticaria	3	2	5
Headache	4	0	4
Vomiting	2	1	3
Dizziness	1	0	1
Others	7	0	7
<b>Total</b>	<b>44 (80%)</b>	<b>11 (20%)</b>	<b>55 (100%)</b>

<sup>a</sup>Mild or moderate intensity.

er's exact test) or with the incidence of the total adverse events ( $P=0.5$ , Fisher's exact test).

#### *Efficacy of the antivenom*

Clinical cure was obtained in 213 patients (96.8%). Fifty-nine of the 223 patients included in this study (26.5%) left the health centre against medical advice and were not examined at day 26; therefore, cure of these patients could not be confirmed. Sequelae were reported in 35 of the 216 patients (16.2%) for whom this information was available, and consisted of necrosis in all cases, most of which were superficial (1–2 cm<sup>2</sup> of skin) and resulted in a limited scar. No amputation was necessary.

Three patients died, a case fatality rate of 1.3%. One patient (male, 30 years old) died after 6 d of intractable haemorrhages; the second (male, 40 years old) died suddenly following substantial alcohol intake during the first day in hospital. The third (female, 30 years old) left the hospital in apparently good health, but was found dead 3 d later. No post mortem diagnosis was available for this case. If the latter 2 deaths, considered to be unrelated to the antivenom, are excluded, a lethality rate of 0.4% is obtained.

Based on the core definition (stage 0 bleeding and WBCT <30 min), the mean time to blood coagulation restoration was 122 ( $\pm 105.2$ ) h (approximately 5 d). The median time was 96 h (4 d). This period roughly corresponds to the minimum period of hospital stay and surveillance required by the protocol. Nonetheless, 25% (first quartile) of the patients took less than 72 h to recover completely and 25% (third quartile) took more than 5 d (120 h).

The criteria for blood coagulability restoration between days 1 and 5 (no sign of bleeding and WBCT <30 min) could be applied for only 158 patients, because (i) 35 subjects did not manifest any clotting disorder, (ii) 12 patients developed a relapse (abnormal test results after an initial return to normal), and (iii) 18 patients had missing or incomplete data. Of these 158 patients with signs of bleeding and/or an abnormal WBCT before treatment, 111 showed blood coagulability restoration within the 5 d monitoring period, according to the haematological criteria. The mean time to blood coagulability restoration in these 111 patients was 24 h (range 1–109 h); the median time was 5.5 h; 25% (first quartile) of the subjects showed blood coagulation restoration in less than 2.2 h, and 25% (third quartile) became normal between 27 h and 5 d. Blood coagulability was restored in the other 47 patients after the monitoring period ( $\geq 6$  d), and the precise time to restoration was not known.

#### **Discussion**

To our knowledge, this was the largest prospective

trial of antivenom treatment to be carried out in sub-Saharan Africa according to GCP guidelines. The main objective was to evaluate the safety of the polyvalent F(ab')<sub>2</sub> equine antivenom administered by intravenous infusion. The intravenous route is not currently used in most African countries. However, administering antivenom intravenously may be more adapted to the requirements of antivenom therapy in these countries where the severity of envenomation and the very precarious medical environment require rapid and effective intervention despite limited technology and means (CHIPPAUX *et al.*, 1996; WARRELL, 1996). The venous route would satisfy these conditions, provided that its safety were good, which was confirmed by this study.

In an attempt to conserve antivenom, we chose to start with an 'affordable' dose of 20 mL (2 ampoules) which could be repeated according to the individual course of envenomation, instead of beginning with higher doses, i.e., 50–150 mL (REID & THEAKSTON, 1984). Indeed, 43% of our subjects recovered after this single infusion. The lack of correlation between the volume of F(ab')<sub>2</sub> administered and the time to cure tended to support the use of such a regimen.

Apart from the one case of anaphylactic-like shock mentioned above, early adverse reactions (9.0%) were benign, and most were compatible with mild hypersensitivity reactions. The overall prevalence of late events was 22.9%, few of which appeared to be attributable to delayed hypersensitivity. Prevalence of serum sickness was low (0.6%) in our series, and had characteristic manifestations. The 2 late serious adverse events (deaths) were both attributable to the envenomation. This low prevalence of serious reactions was certainly attributable to the purity of the F(ab')<sub>2</sub> antivenom, which is devoid of highly immunogenic albumin,  $\alpha$ - and  $\beta$ -globulins, other high molecular weight proteins, and aggregates. The incidence of adverse reactions was lower than generally reported in the literature when F(ab')<sub>2</sub> is used. Nevertheless, our results were very similar to those obtained by MEYER *et al.* (1997) in north Nigeria with the same product, Ipser Africa<sup>TM</sup>. Subsequent to earlier reports in the literature, the purity of F(ab')<sub>2</sub> has been greatly improved, which could explain the patients' good tolerance of it.

#### *Efficacy*

The efficacy of treatment was based on simple clinical criteria [prevalence of sequelae (amputation) and mortality], as well as haematological indicators (bleeding and WBCT). Absolute efficacy cannot be established in comparison with an untreated control group, for obvious ethical reasons based on previous evidence of antivenom efficacy (WHO, 1981; PUGH & THEAKSTON, 1987; CARDOSO *et al.*, 1993). Meta-analysis of case controls is impossible owing to the absence of standardized medical files in African health centres.

Evaluation of efficacy can, nevertheless, focus on comparing the results obtained in a large standardized field trial (having sufficient statistical power) with those reported in the literature (PUGH & THEAKSTON, 1987). However, this literature is relatively limited, dealing at most with a cluster of case reports, often using different methods and criteria.

Observations in the same centre, before the introduction of the trial treatment, also can be used as a basis for comparison, although with certain methodological reservations (owing to differences in the populations and diagnostic and prognostic criteria). The effect of certain biases (population or seasonal variations) could be minimized over a fairly long period with a sufficient sample size, as confirmed by the homogeneity of the cases reported in different places and at different times by CHIPPAUX *et al.* (1996) and CHIPPAUX (1988).

In the absence of standardized treatment, the prevalence of amputations varies between zero and 3%, and snake bite case fatality rates are between 2% and 28%

(CHIPPAUX *et al.*, 1981). Compared to these data, the absence of amputation and the low absolute case fatality rate (1.3%) reported in our study are very much in favour of treatment with polyvalent F(ab')<sub>2</sub> equine antivenom administered by intravenous infusion of repeated doses of 20 mL (1 mL neutralizing 20 LD<sub>50</sub> of *E. ocellatus* venom). Comparison of mortality rates in the same centres over the years preceding our trial also supports the use of polyvalent F(ab')<sub>2</sub> equine antivenom (Table 4).

The reference test of choice for the sub-Saharan region of Africa is probably the WBCT 20 min test, as described by WARRELL *et al.* (1977), or the 30 min variant, as in our study. We have shown that the prolongation of the whole-cell clotting time constitutes an early sign of envenomation, as it is often altered within an hour of the bite and always altered before appearance of the first clinical sign of bleeding. The relationship between eventual signs of bleeding and prolonged clotting time was very significant ( $P=0.004$ ,  $\chi^2$  test). The 30 min

Table 4. Mortality rates following snake envenomation in the main study centres in Cameroon

Centre	Period	Previous epidemiological studies		Present clinical study	
		No. of subjects	Mortality (%)	No. of subjects	Mortality (%)
Garoua Provincial Hospital (reference hospital)	1988-1992	200	7 (6.2-8.0) <sup>a</sup>	35	1.6
Toubo Hospital	1986-1993	476	9.7 (4.9-23.9)	38	4.3
Lara Dispensary	1989-1993	510	0.7 (0-1.2) <sup>a</sup>	67	0
Doukoula Dispensary	1989-1993	296	2 (0-4.6) <sup>a</sup>	60	0
Total	-	1482	4.7	200	1.1

<sup>a</sup>Most patients treated with one vial of antivenom (exceptionally with 2).

A high-powered, randomized trial to compare relative efficacy with other antivenoms, like the new ovine monovalent antivenom, would be of interest. A trial in northern Nigeria (MEYER *et al.*, 1997) showed that both monospecific Fab antivenom and polyvalent F(ab')<sub>2</sub> (Ipser Africa™) were safe and effective. However, as unidentified snakes may be involved in envenomations over different ecological areas, polyvalent antivenom has wider applicability.

It is possible that our results could be explained by the inclusion of a large proportion of mildly envenomed patients, or rapid implementation of antivenom treatment. In this trial, the mean interval between bite and admission to hospital was less than 12 h, which is brief compared to the 2 d interval reported by MEYER *et al.* (1997). This short time to admission may explain both the mild symptoms (because clinical examination was performed early in the course of envenomation) and the good efficacy of treatment (because it was applied early).

#### Surveillance indicators

Oedema develops rapidly and generally reflects the severity of the snake bite. This symptom is a relatively specific and probably fairly sensitive indicator of envenomation, and develops after 93% of viper bites (BLAYLOCK, 1983; REID & THEAKSTON, 1983). However, it is slow to resolve, even after haematological cure, making it a poor indicator of the clinical course. There are 2 possible explanations for the highly significant relationship observed between the time before admission and the severity of oedema. First, oedema develops gradually, so its degree is proportional to the time before admission. Second, the swelling adds to the patient's anxiety which, beyond a certain stage, causes the patient to seek medical advice, regardless of any initial reluctance.

One indisputable sign of severity is persistent bleeding, especially at a site distal from the bite. Persistent bleeding corresponds to a complicated viper envenomation, with a poor prognosis. The relationship between the time before admission and the severity of bleeding was significant ( $P=0.018$ ,  $\chi^2$  test). Signs of external bleeding (stage 4) constitute a marked incentive to seek immediate medical attention. However, in such cases, it is often already too late, because a haemorrhagic syndrome is generally poorly treated in Africa. Detection of microscopical haematuria by urine reagent dipsticks is potentially useful, as it correlates excellently with external bleeding. Although this could be used systematically as a screening test for early detection of haemorrhagic syndromes, the results are difficult to interpret in areas like rural Africa where urinary schistosomiasis is endemic.

WBCT test performed well, with a positive predictive value of 85% and a specificity of 92% (WARRELL *et al.*, 1977). One-quarter of the subjects admitted to the health centre with a WBCT greater than 30 min, presented with bleeding at stage 2 or more, despite treatment. Finally, the WBCT is very simple to perform in an otherwise poorly equipped, rural dispensary. This test should be more widely used as a diagnostic indicator in Africa, especially in peripheral dispensaries, since it can be used both to evaluate the severity of the snake bite and to monitor the patient's course.

#### Conclusions

We have established the safety of intravenously administered polyvalent F(ab')<sub>2</sub> equine antivenom. An intermittent infusion schedule, using low doses of 20 mL that were repeated depending on the clinical and biological markers of envenomation, was used. Among the 223 severely envenomed patients enrolled, anaphylactic shock and serum sickness were reported in less than 1%. Efficacy was assessed in envenomations treated soon after the bite. The case fatality rate was 1.3%. Early treatment in rural dispensaries was associated with the use of lower doses and the occurrence of fewer reactions. In addition, the use of the 30 min WBCT test has been shown to be valuable for monitoring clinical status of the envenomed patient in rural dispensaries or provincial hospitals in Africa.

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## Short Report

### Lengthy persistence of ciguatoxin in the body

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**Keywords:** ciguatera, ciguatoxin, *Lutjanus* spp.

Ciguatera, caused by ciguatoxic coral reef fish, is the commonest 'toxic' illness resulting from seafood consumption in Hong Kong (CHOI & WONG, 1994). During 1988–1992, 60% of the outbreaks were caused by the *Lutjanus* spp. (e.g., mangrove snapper and black fin red snapper). Ciguatera generally presents as gastrointestinal and neurological complaints. The former usually persist for a few days. Neurological symptoms, which may appear early or several days after the gastrointestinal symptoms have resolved, may persist for weeks or even months. For unknown reasons, symptoms may recur following the ingestion of alcohol and, especially, reef fish (MINES *et al.*, 1997).

#### Case report

A 40 years old male health worker experienced symptoms of ciguatera early in 1996 after eating the head of some coral reef fish fried in batter. The gastrointestinal symptoms (colicky abdominal pain and diarrhoea) and headache gradually subsided during one week, but the neurological symptoms (paraesthesia in perioral area and the extremities, myalgia and malaise) and arthralgia persisted for a month. He had not subsequently eaten reef fish. Previously he used to eat reef fish weighing un-

der 2 kg (usually approximately 35 g of the flesh cooked by steaming) about 4 times a year. In March 1998 he drank half a pint [c. 300 mL] of beer for the first time since mid 1995. The following evening, he experienced a relapse of neurological symptoms and arthralgia, all of which improved within one week. Since 1996, he had also noticed easily-induced paraesthesia in the extremities, e.g., when sitting with his arms resting on the arm support of a chair or with his legs crossed.

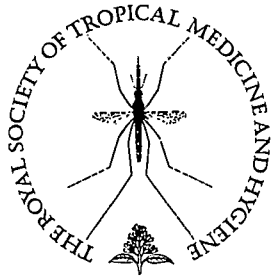
#### Discussion

At least 5 different toxins have been implicated in ciguatera (MINES *et al.*, 1997). The neurological symptoms can largely be accounted for by the effects of ciguatoxin on the voltage-dependent sodium channels in both nerve and muscle cells. Ciguatoxin is heat-stable and lipid-soluble. How the body handles this and other toxins is not known. However, there is increasing clinical evidence that ciguatoxin may persist in the body. The case described here had ciguatera 2 years ago and experienced a relapse of symptoms after drinking alcohol. Chronicity of neurological symptoms, including chronic fatigue, has been well described (PEARN, 1997). Subjects with previous episodes of poisoning may have increasingly severe and prolonged symptoms after further exposure.

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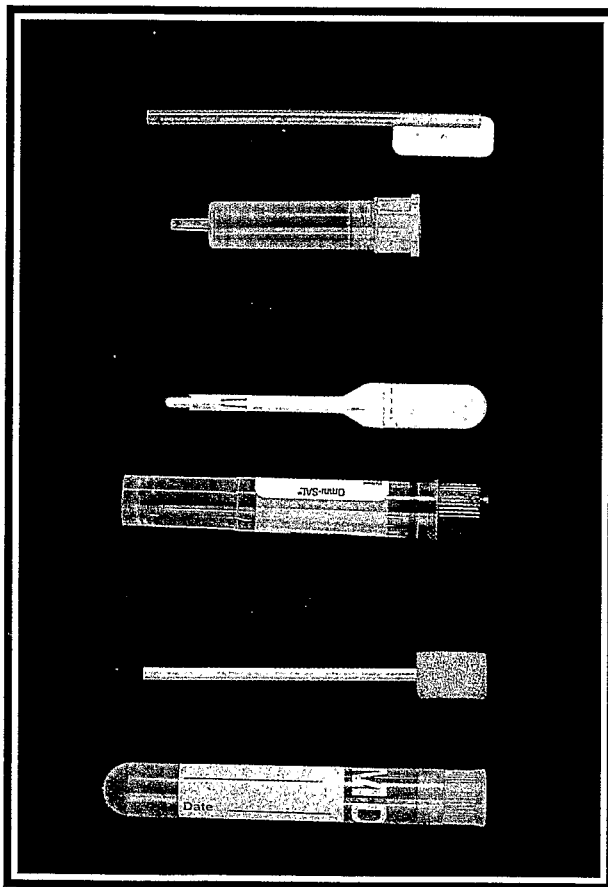
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