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SHORT REPORT: TREATMENT OF SNAKE ENVENOMATIONS BY A NEW POLYVALENT ANTIVENOM COMPOSED OF HIGHLY PURIFIED F(ab')₂: RESULTS OF A CLINICAL TRIAL IN NORTHERN CAMEROON

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Abstract. A clinical trial was conducted in 2 health centers in northern Cameroon to assess the safety and efficacy of a new polyvalent antivenom composed of highly purified and pasteurized F(ab')₂ (FAV-Africa). Forty-six patients with objective signs of envenomation, including 67% with hemorrhage, were included in the study. Each patient received at least 20 ml of FAV-Africa by direct, slow intravenous injection; 172 10-ml ampules were administered. All patients were clinically cured after treatment. Two patients (4.3%) showed minor immediate adverse events that may have been related to FAV-Africa (induration, light-headedness); no other treatment-related adverse event occurred. No patient had serum sickness. This trial confirms the safety of FAV-Africa administered by intravenous injection and its efficacy in the treatment of snake envenomations in sub-Saharan Africa.

Antivenom immunotherapy is the only effective treatment against envenomations. In Africa, however, due to the restricted availability of antivenoms, usage constraints, and the fear of adverse reactions, use of serum therapy has been limited.¹ The recent development of antivenoms made of purified fragments of IgG with decreased risk of adverse reactions should improve acceptability of their use under field conditions. FAV-Africa (Pasteur Mérieux Connaught, Lyon, France) is a new highly purified equine F(ab')₂ whose manufacturing process involves several additional purification steps compared with those classically used to produce other antivenoms. The venoms involved in the production of FAV-Africa are the same as those used in IPSE-Africa (Pasteur Mérieux Connaught), which include that from *Echis leucogaster* but not *E. ocellatus*.² It is administered by direct, intravenous injection that results in a rapid distribution of antibodies, and also reduces the material and materials necessary for injection.

In this study, which was conducted from January to June 1996 in 2 health centers in northern Cameroon (Garoua Hospital and Doukoula Dispensary), we assessed the safety and efficacy of FAV-Africa in the treatment of snake envenomation. The protocol was approved by the National Ethic Committee of Cameroon prior to initiation of the study.

Sixty-one patients reporting to the 2 centers for suspected snake bite underwent a clinical examination, as described by Chippaux and others.² Briefly, the clinical examination was standardized for edema and bleeding, and the whole blood clotting time (WBCT) was measured according to the method described by Warrell and others,³ as modified by Chippaux and others.² Forty-six patients (22 at Garoua and 24 at Doukoula) with objective signs of envenomation (i.e., edema, and/or bleeding and/or a WBCT \geq 30 min) were included in the study after providing written informed consent. Snakes were brought in by the victim in 31 cases. *Echis ocellatus*, a Viperidae that can induce severe hemorrhage, was incriminated 27 times and represented 87% of identified snakes, which is similar to results obtained in a previous survey.² The mean interval between the snake bite and arrival at the health center was 17 hr; 50% of the patients

arrived within 4 hr of being bitten and 23% arrived more than 12 hr later. All but 1 patient presented with edema. Bleeding was observed in 21 patients (46%), and blood was uncoagulable (WBCT > 30 min) in 31 patients (67%).

Twenty milliliters of FAV-Africa were administered to all patients by slow (5 min) direct intravenous injection (DIV). Subjects were monitored for 1 hr, and a second clinical and laboratory assessment was performed 2 hr after injection. In the case of spontaneous bleeding, the same treatment dose was administered by DIV. Further clinical (temperature, blood pressure, pulse rate, measure of edema) and laboratory assessments (hematuria, proteinuria, and WBCT) were performed every day; in the case of spontaneous bleeding (non-traumatic bleeding from the site of the bite, the gums, a previous wound or scar, petechie, echymosis, epistaxis, hematuria, hematemesis) and/or a WBCT > 30 min, a similar treatment dose was administered. Patients could leave the hospital after clinical cure, but were asked to return 4 weeks after the first administration of FAV-Africa (day 26) for evaluation of safety. Clinical cure was obtained in all 46 patients; a total of 1,720 ml of FAV-Africa was administered (37 ± 4 ml per patient). The mean hospital stay was 6.6 days, and the mean time to resolution of hemorrhaging was 1.1 days.

Concerning safety, all events occurring after treatment were reported. We defined immediate events as those occurring within 30 min of FAV-Africa administration, early events from 30 min to 12 hr, semi-delayed events between 12 and 48 hr, and delayed events from 48 hr onwards. Of the 46 patients included, 5 were lost to follow-up after cure, 1 before day 5. Four patients presented with a serious adverse event, none of which was attributed to treatment. One child developed Wolkman's syndrome (ischemic contraction of muscles and tendons) following extensive edema at the site of the bite. Two adults developed hemorrhagic complications (meningeal hemorrhage without sequelae and gastrointestinal hemorrhage). One patient, to whom a tourniquet had been applied during the 12 hr between being bitten and admission to the center, presented with gangrene that necessitated amputation of a leg. Two patients (4%) presented with a minor immediate event considered by the investigator



to be possibly attributable to FAV-Africa (slight induration at the FAV-Africa injection site and moderate light-headedness). Four patients experienced at least 1 early event (pruritus at the venipuncture site, hematemesis, epistaxis, lower back pain, hematoma at the bite site, and an increase in edema). Seven patients presented a semi-delayed event (fever, necrosis at the bite site, meningeal hemorrhage, epistaxis, and hematuria). Of the 39 patients examined on day 26, 10 presented a delayed adverse event (diarrhea, headache, hematoma or pruritus at the venipuncture site, skin rash, vertigo, melena, Wolkman's syndrome, and necrosis at the bite site). No early, semi-delayed, or delayed events were considered to be related to FAV-Africa; in particular, no patient presented with serum sickness or serum-like sickness.

The efficacy of FAV-Africa can be inferred from data obtained before the antivenom trials, first in Garoua between 1988 and 1992 (200 cases, approximately 10–20% treated with antivenom, and 14 deaths) and then in Doukoula between 1989 and 1992 (296 cases, 80–90% treated with a low dose of antivenom administered intravenously, and 6 deaths).²

These results demonstrate the favorable safety profile of FAV-Africa compared with other less purified preparations. Under similar conditions, treatment with the antivenom IPSER-Africa, which is less purified than FAV-Africa, had a prevalence of adverse effects ranging from 7.6% to 12%.²⁻⁴ Nevertheless, during our study, we observed a significant relationship between the frequency of adverse effects and the volume of FAV-Africa injected ($P < 0.001$, by Mantel-Haenszel chi-square test). However, most reactions (hematoma at the venipuncture site, pruritus at the site of the bite site, diarrhea, lower back pain, agitation) did not appear to correspond clinically to signs and symptoms of horse protein intolerance, and other symptoms (fever, headache, hematuria) were explained by the presence of an intercurrent disease (malaria and schistosomiasis). Furthermore, there is an obvious confounding factor since the volume of protein injected was dependent on the severity of the envenomation.

This study confirmed the safety and efficacy of FAV-Africa administered by DIV for the treatment of snake enven-

omation. This antivenom could be used as a first-line treatment for confirmed envenomation, even in a peripheral health center. Moreover, its good safety profile enables it to be used broadly, even at early stages, or when the severity of envenomation has not yet been established. We attempted to define a simple therapeutic protocol that was both accessible to overburdened personnel and feasible in an under-equipped environment. The administration of 20 ml of FAV-Africa, with a repeat treatment 6 hr later in the absence of improvement of a hemorrhagic syndrome, or earlier in the case of deterioration, appears sufficient in the majority of cases. Clinical surveillance of bleeding should be completed by WBCT measurements that can predict a possible hemorrhagic syndrome and confirm its resolution.

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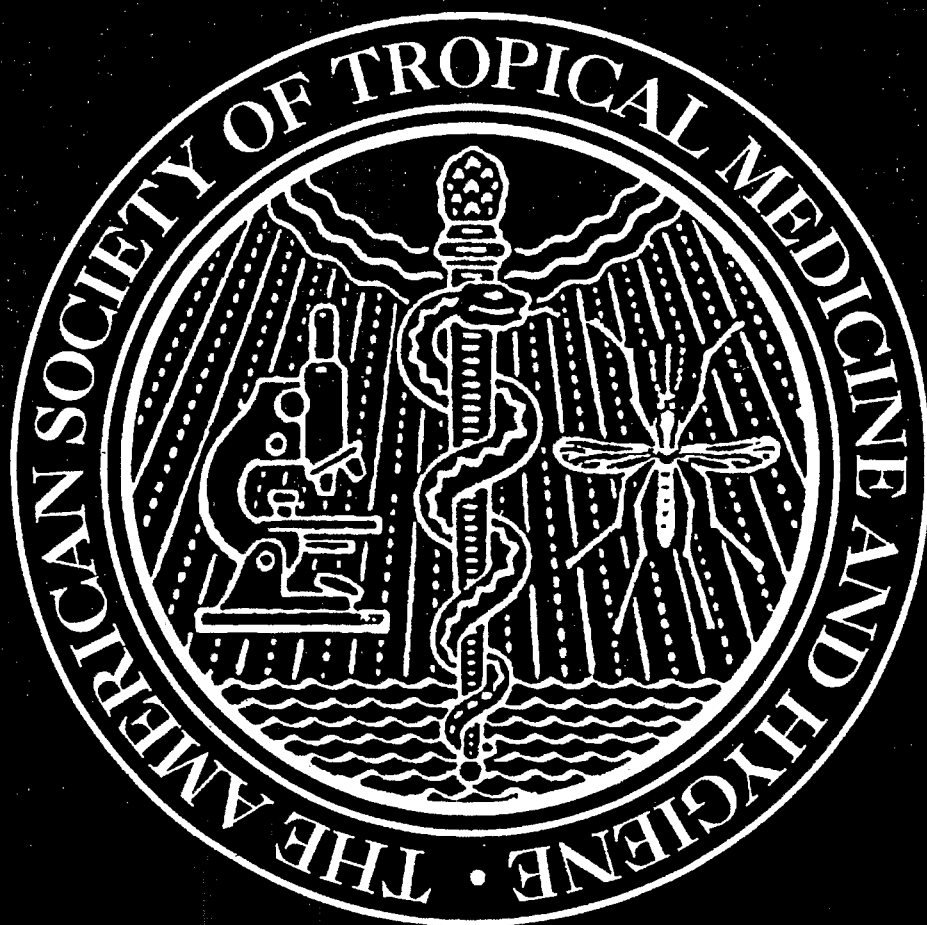
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