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THE DEVELOPMENT AND USE OF IMMUNOTHERAPY IN AFRICA

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J.-P. Chippaux. The development and use of immunotherapy in Africa. *Toxicon* **36,** 1503–1506, 1998. —The immunotherapy was recently developed due to the improvement of purification techniques of antivenoms and results of the research in toxicology and pharmacology. The utilisation of highly purified IgG fragments leads to a better tolerance and a higher efficacy. Snake envenomations constitute in Africa, as in many tropical countries, an important public health problem. The annual incidence of snakebites reaches 1 million and the annual mortality is about 20,000 deaths. Less than 25% of the antivenom needs are effectively covered and, probably in most of envenomations, used at insufficient doses. The treatment of snakebites would be improved by better knowledge on snakebite epidemiology, standardisation of treatment and training medical staff, and development of new financial procedures for antivenom supply.

INTRODUCTION

Since the discovery of immunotherapy one century ago, progress in this area has been moderate. Improvements have centered around the tolerance and the efficiency of antivenom. In contrast, notably in Africa, the availability of antivenom has decreased since the 70's and therapeutic protocols are non-existent or inappropriate. This is due to a lack of epidemiological data, disorganisation of health services and the high cost of antivenom with respect to the income of rural populations.

IMMUNOTHERAPY: A NEW CONCEPT FOR AN OLD TOOL

The objectives of immunotherapy are (i) to administer the smallest possible quantity of heterologous proteins to improve tolerance and ii) to use the greatest quantity of antibodies to increase efficiency.

This apparent contradiction can be avoided by improving the purification of the antivenom (precipitation, cleavage of IgG, filtration, chromatography) and by using more rigorous therapeutic protocols (intravenous administration of antivenom, standardisation

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Table 1. Comparison between IgG, Fab and $F(ab')_2$

	IgG	$F(ab')_2$	Fab
Obtainment	precipitation	precipitation + pepsin	precipitation + papain
Distribution	> 3 h	3 h	1 h
Elimination	> 100 h	60 h	10 h
Tissue affinity	1	2	5
Complement reaction	yes	no	no
Immunologic affinity	1 to 2	1 to 2	1
Excretion	immune tissue	immune tissue	kidney

of diagnosis and supervision indicators, therapeutic adjuvants). More recently, the choice of the antibody [IgG, Fab and $F(ab')_2$] became controversial. Each fragment has its advantages and disadvantages (Table 1). IgG should not be used because of the frequency of extensive severe adverse effects. Fab fragments present advantages of a more rapid and important distribution in tissues. On the other hand, the $F(ab')_2$ fragments last longer in the organism allowing delayed readministration and decreased doses of antivenom. Furthermore, $F(ab')_2$ fragments, in contrast to Fab fragments, are not eliminated through the kidney and thus do not cause renal complications.

IMMUNOTHERAPY IN AFRICA: FAILURE OF A POWERFUL TREATMENT

The sale of antivenoms has declined by 60 to 80% during the last 20 years. Furthermore, the actual number of doses sold would not have covered even quarter of the estimated needs. Several causes could explain this.

The epidemiology of snake bites is poorly understood. The incidence is unknown and highly endemic regions have not been delimited. Consequently, real needs are not easily evaluated.

The treatment of envenomation is not standardised and practices are mostly empirical and irrational (sub-cutaneous injection around the bite, administration of half-doses in children, doses determined independently of both the envenomation or severity of clinical signs).

Health centres are generally poorly stocked in appropriate therapies (antivenoms and symptomatic medicines). The distribution of vials of antivenom is limited because of the risk of losses in the case when out-of-date vials must be discarded. In addition, users, therapists, as well as patients, do not know where they can obtain antivenom.

Finally, the cost of one vial of antivenom represents approximately one month of income for a family of a peasant. This discourages the buying of more than one vial even when two to four vials are necessary.

SNAKE BITES IN AFRICA: APPRAISAL OF NEEDS

According to surveys performed in rural areas, the number of snake bites (=incidence) ranges from 150 to 600 cases per 100,000 inhabitants per year. Variations can be attributed to the methodological and environmental differences. In addition, some human occupations induce the man–snake encounter. Approximately 50 to 75% of snake bites lead to an envenomation (=morbidity) necessitating antivenom therapy. Finally, depending on the delay before consultation and the efficiency of treatment management, lethality can vary from 1 to 25% of envenomations.

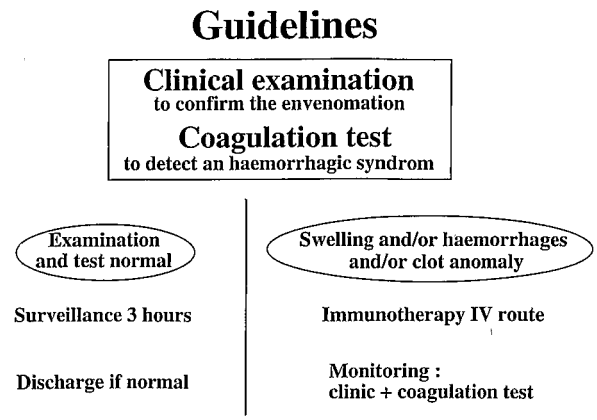

Fig. 1. Proposed guidelines for envenomation treatment in Africa.

In Africa, the population at risk ranges from 400 to 450 million people, predominantly in rural areas. The number of snake bites can therefore be estimated at 600 000 to 1 million cases per year. Between 300 000 and 600 000 patients are envenomed necessitating one to four vials of antivenom (an average of 2.8 according to recent clinical trials to be confirmed). The number of deaths is probably about 20 000 per year.

In any case, the annual number of antivenom vials required is certainly higher than 500 000, whereas less than 100 000 are currently sold.

TREATMENT OF SNAKE BITES IN AFRICA: PERSPECTIVES

Three kinds of measures can be suggested to improve the treatment of snake bites in Africa.

Epidemiological data

To better understand the epidemiology of snake bites in Africa, an obligatory and systematic notification system and surveys based on rigorous methodology are needed. Such data would allow the proposal of a best distribution of the antivenom in the space and time permitted.

Improvement of treatment

The improvement of treatment is necessary and comprises two aspects that have to be developed without increasing the cost of antivenom. On the one hand, it is important to standardise the treatment (intravenous administration of the antivenom, dose of the antivenom, association of adjuvant medicines) and its supervision (clinic and biological indicators, simple and adapted to the African rural context). On the other hand, it is necessary to promote the training of the medical staff and its information, using guidelines (Fig. 1).

Organising the financing of the treatment

Several solutions, that can be interrelated, should be explored. It is possible to negotiate a reduction in the sale price by the producer, compensated by a higher cost of the corresponding product in developed countries. The marketing and distribution of drugs (antivenoms and symptomatic medicines) could be improved by a better knowledge of commercial networks (wholesalers, retailers) increasing the availability of products and by proposing new commercial practices (replacement of out-of-date vials). Finally, it is necessary to research adequate financing procedures (support by State or local collectives, sponsoring by companies, community participation).

Using *ad hoc* commercial and therapeutic strategies, it should be possible to develop immunotherapy in Africa, avoiding a significant increase in the cost and thus to reduce by about 90% the lethality of snake envenomations.

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