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Stability, distribution and use of antivenoms for snakebite envenomation in Latin America: Report of a workshop

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ABSTRACT

The issues of antivenom stability and distribution, and the training of health staff in the correct use of antivenoms in Latin America were discussed in a workshop held at Instituto Clodomiro Picado, Costa Rica, in September 16–19, 2008, under the auspices of the program CYTED. Participants from public antivenom production laboratories of the region, together with representatives of the Ministries of Health, from Argentina, Paraguay, Brazil, Bolivia, Perú, Ecuador, Colombia, Venezuela, Panamá, Costa Rica and Nicaragua participated in the event. Technical advances in the study of antivenom stability and in the design of novel formulations aimed at generating products of higher stability were presented. In addition, antivenom acquisition and distribution systems in every country were presented and discussed, together with novel tools that could be useful for improving antivenom distribution, such as the software SIGEpi, developed by the Pan American Health Organization. The issue of the cold chain, as well as the most frequent causes of misuse of antivenoms in the region, were also analyzed. Finally, the experiences of training programs for health staff on the correct use of antivenoms in snakebite envenomation treatment in Latin America were presented. It was concluded that, in addition to the fostering of antivenom production and quality control, renewed efforts should be implemented at improving the stability, distribution and correct use of antivenoms in the region.

1. Introduction

Snakebite envenomations constitute a significant public health problem in Latin America (Fan and Cardoso, 1995; Gutiérrez, 1995; Chippaux, 1998; Warrell, 2004; Kasturiratne et al., 2008). Antivenoms, the only validated treatment for these envenomations, are produced in the region by a heterogeneous universe of manufacturers which includes laboratories predominantly belonging to public institutions and others located in the private realm (Gutiérrez et al., 2007). Some countries and subregions in Latin America are self-sufficient in terms of antivenom supply, whereas others are not. A regional project, supported by the organization CYTED ('Ciencia y Tecnología para el Desarrollo'), started in 2006 with the aim of strengthening the endogenous capacity of public institutions in the region to produce and control antivenoms. This network, which includes laboratories and groups from 10 countries, has a research component, as well as a capacity-building component based on training exchange activities and organization of annual workshops. Technical workshops on antivenom production and quality control were organized in 2006 and 2007 at Instituto Butantan (Brazil) and Instituto Clodomiro Picado (Costa Rica), respectively (Gutiérrez et al., 2007).

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The success of the use of antivenom in the treatment of snakebite envenomations involves other issues in addition to the production and quality control of these immunobiologicals. These issues, often neglected in the analyses of this subject, include the stability and distribution of antivenoms to the regions where they are going to be used, as well as the training of the health staff in the correct use of these drugs. This report presents the discussions and conclusions of a workshop on the stability, distribution and training in the use of antivenoms in Latin America, which was held at Instituto Clodomiro Picado, Costa Rica in September 16–19, 2008.

2. Stability of antivenoms and the cold chain

Stability studies of liquid antivenoms manufactured in Costa Rica, Brazil, Peru and Colombia were presented. These studies confirmed the stability of various liquid preparations stored for three years at $5 \pm 3\,^{\circ}C$. Since different types of antivenoms, i.e. whole IgG and $F(ab')_2$ antivenoms, are manufactured by different laboratories, the need to have stability studies by each manufacturer and product formulation was emphasized. Two issues that remain open for investigation are (a) what is the actual shelf-life for liquid antivenom preparations?, and (b) what is the effect on antivenom stability of short-term interruptions in the cold chain during the storage of these products?. Preliminary evidence was presented supporting the contention that the shelf-life of liquid preparations stored at $5 \pm 3\,^{\circ}C$ may be higher than three years, an issue that requires further investigation. This is particularly important in the case of antivenoms for envenomations that occur infrequently, such as those induced by *Lachesis* sp. and *Micrurus* sp. In these cases, it is common that antivenoms are not used at the time of expiry; since these antivenoms are precious medicines, difficult to produce and scarce, the possibility of extending their shelf-life is very important and needs to be documented. A similar situation occurs with freeze-dried antivenoms, whose shelf-life has been estimated as being five years (Theakston et al., 2003). There is circumstantial evidence indicating that there shelf-life is likely to be more prolonged.

The results of preliminary studies with liquid antivenoms in which the cold chain was interrupted for short time intervals also evidenced that stability was not significantly affected in these circumstances. This is a relevant finding since failures in power supply often result in such temporary interruptions in the cold chain. Moreover, the effects of temporary freezing of antivenoms have to be also considered and investigated, since this might occur during storage and transportation. Alvaro Segura and María Herrera, from Instituto Clodomiro Picado, presented the results of investigations aimed at developing new formulations for liquid and lyophilized antivenoms, in order to improve their stability. Promising results have been obtained with the use of sorbitol in the stabilization of liquid preparations, in order to store them at temperatures of around $25\,^{\circ}C$. Overall, the results presented reinforce the need to perform more detailed studies on the stability of antivenoms in the region. The subject of cold chain was presented by Carmen Silvera, from Brazil, who discussed all aspects related with the correct storage and transportation of antivenoms and the most common problems found in the region concerning the maintenance of a cold chain. Due to a number of difficulties for keeping a cold chain, especially in some rural regions of Latin America, the need for a quality control of the cold chain, including the regular monitoring of temperature, was stressed.

3. Distribution of antivenoms

The situation of antivenom distribution to the hospitals and other health facilities in the various countries in the region was analyzed in detail.

3.1. Brazil

The situation of acquisition and distribution of antivenoms in Brazil was presented by Hui Wen Fan and Carmen Silvera. This country, which has a long tradition of antivenom manufacture, created a National Program for Self-Sufficiency in Immunobiologicals, which includes antivenoms, in 1985. In addition, a National Program for the Control of Accidents by Venomous Animals was established in 1986. This program includes: (a) epidemiological surveillance; (b) modernization of technology and infrastructure for antivenom production; (c) standardization of diagnostic and therapeutic parameters; (d) analysis of the geographical distribution of venomous animals in the country; and (e) introduction of permanent training programs for health personnel. A total of 29,121 snakebite cases were reported in Brazil in 2006. There are four public laboratories that manufacture antivenoms, i.e. Instituto Butantan, Fundação Ezequiel Dias (FUNED), Instituto Vital Brazil, and Centro de Produção e Pesquisa de Imunobiológicos (CPPI). Antivenom production by these laboratories is coordinated with the needs of the Ministry of Health and the annual production is organized accordingly. A total of 424,763 antivenom ampoules were produced in 2007. The acquisition process is centralized and antivenoms are received by the National Center for the Distribution and Storage of Immunobiologicals (CENADI). After the quality control is performed by the National Institute for the Quality Control in Health (INCQS), the distribution of antivenoms is authorized. Such distribution process is a decentralized one, and is based on the antivenom needs of the various regions; antivenoms are distributed to the State Secretaries of Health, then to the Regional Offices of Health, then to the Municipal Secretaries and finally to the Health Services.

The planning of antivenom distribution is based on the following equation:

$$N = [(x \cdot y) + (\alpha + \beta)] - \delta$$

where:

N = number of vials to be distributed.

x = number of snakebite cases.

y = mean number of antivenom vials used per patient.

α = estimated underregistration of snakebite cases.

β = technical losses of antivenom (expired and/or incorrectly stored or transported).

δ = vials of antivenoms in stock in that region.