Toxicon 76 (2013) 63–76

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Review

Pathogenic mechanisms underlying adverse reactions induced by intravenous administration of snake antivenoms

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ARTICLE INFO

Article history:
Received 30 May 2013
Received in revised form 1 September 2013
Accepted 11 September 2013
Available online 20 September 2013

Keywords:
Snake antivenom
Adverse reactions
Early reactions
Anaphylactic reactions
Serum sickness
Anaphylactoid reactions

ABSTRACT

Snake antivenoms are formulations of immunoglobulins, or immunoglobulin fragments, purified from the plasma of animals immunized with snake venoms. Their therapeutic success lies in their ability to mitigate the progress of toxic effects induced by snake venom components, when administered intravenously. However, due to diverse factors, such as deficient manufacturing practices, physicochemical characteristics of formulations, or inherent properties of heterologous immunoglobulins, antivenoms can induce undesirable adverse reactions. Based on the time lapse between antivenom administration and the onset of clinical manifestations, the World Health Organization has classified these adverse reactions as: 1 – Early reactions, if they occur within the first hours after antivenom infusion, or 2 – late reactions, when occurring between 5 and 20 days after treatment. While all late reactions are mediated by IgM or IgG antibodies raised in the patient against antivenom proteins, and the consequent formation of immune complexes, several mechanisms may be responsible for the early reactions, such as pyrogenic reactions, IgE-mediated reactions, or non IgE-mediated reactions. This work reviews the hypotheses that have been proposed to explain the mechanisms involved in these adverse reactions to antivenoms. The understanding of these pathogenic mechanisms is necessary for the development of safer products and for the improvement of snakebite envenomation treatment.

1. Introduction

Snake antivenoms are formulations of immunoglobulins, or immunoglobulin fragments, purified from the plasma of animals immunized with snake venoms. Their parenteral administration is the mainstay treatment for snakebite envenomation (WHO, 2010a), which is an important, albeit neglected, health problem in many regions of the world (Kasturiratne et al., 2008; Williams et al., 2010; Gutiérrez, 2012). Antivenom immunoglobulins bind and neutralize, through various mechanisms, the toxins present in the venoms which are responsible for the pathophysiological alterations associated with these envenomations (Gutiérrez et al., 2011).

In addition to their therapeutic effect, snake antivenoms can also induce undesirable effects, whose incidence and severity vary between different products (Gutiérrez et al., 2011). The pathogenesis of adverse reactions to antivenoms is not entirely understood. However, it has been related to: 1 – Factors depending on the manufacturing practices, such as contamination of the formulation with endotoxins (Acconci et al., 2000) or viruses (Burnouf et al., 2004; WHO, 2010a); 2 – factors depending on the physicochemical characteristics of the antivenom, such as purity (Segura et al., 2013) and content of protein aggregates (Frommhagen and Fudenberg, 1962); and 3 – factors

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0041-0101/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.toxicon.2013.09.010

depending on the immunochemical characteristics of heterologous immunoglobulins of antivenoms, such as anticomplementary activity (Sutherland, 1977) and immunogenicity (Herrera et al., 2005; León et al., 2008; Sevcik et al., 2008; Redwan et al., 2009).

Studies on adverse reactions induced by antivenoms have been previously discussed, but conclusive evidences on their mechanisms have not been reached (Lalloo and Theakston, 2003; Morais and Massaldi, 2009; Gutiérrez et al., 2011). Moreover, new findings on this subject have been published, and discrepancies regarding the nomenclature used to designate the different types of adverse reactions have appeared. In this context, the present work presents an updated view of the pathogenic mechanisms involved in the adverse reactions occurring after the administration of snake antivenoms.

2. Nomenclature of adverse reactions

In 1963, Gell and Coombs proposed a nomenclature to classify allergic reactions based on the mechanisms of the underlying disease (Gell and Coombs, 1963). Afterward, they used this arrangement to classify drug-induced hypersensitivities (Coombs and Gell, 1968). According to the Gell-Coombs classification, adverse reactions induced by antivenoms correspond to type I or type III hypersensitivities, depending on whether the antibody mediating the reaction is IgE or IgG, respectively.

In 1981, the World Health Organization (WHO) classified the adverse reactions to antivenoms on the basis of the time lapse between antivenom administration and clinical manifestations of undesirable effects. Such classification includes: 1 – Early reactions, if they occur within 24 h after antivenom administration, or 2 – late reactions occurring between 5 and 24 days after antivenom administration. In turn, early reactions were classified as either anaphylactic or anaphylactoid, depending on whether the reaction is mediated by IgE (anaphylactic) of by other mechanisms (anaphylactoid) (WHO, 1981).

More recently, the World Allergy Organization (WAO) proposed a new global nomenclature for allergy, which is based on the mechanisms initiating the reaction (Johansson et al., 2004). According to this system, the terms "anaphylactic reactions", "anaphylactoid reactions" and "late reactions" proposed by WHO (1981), are substituted by the terms "IgE-mediated allergy", "Immediate hypersensitivity" and "IgG-mediated allergy", respectively.

In 2010, the WHO published the Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins (WHO, 2010a). In this document, adverse reactions are classified as: 1 – early reactions (i.e. pyrogenic reactions and anaphylactic reactions), or 2 – late reactions (i.e. serum sickness). Moreover, the term "anaphylactic reaction" is used to refer to both "non-IgE-mediated reactions" and "IgE-mediated reactions", thus eliminating the term "anaphylactoid reaction" (WHO, 2010a).

Nowadays, both the Gell-Coombs classification and the WHO classification published in 1981 are considered outdated (Descotes and Choquet-Kastylevsky, 2001; Rajan, 2003). Therefore, some researchers have implemented the WAO nomenclature to describe the adverse reactions induced by antivenoms (e.g. Isbister et al., 2008). However, many groups involved in the manufacture and study of antivenoms continue to use the nomenclature derived from the WHO classification published in 1981 (Chippaux et al., 2007; Williams et al., 2007; León et al., 2008; Simpson, 2008; Thiansookon and Rojnuckarin, 2008; Caron et al., 2009; Morais and Massaldi, 2009). For the sake of clarity and uniformity, the nomenclature proposed by the WHO guidelines published in 2010 is used in this work.

3. Early reactions

Early reactions to antivenom administration comprise the group of adverse manifestations which occur within 24 h after starting the intravenous administration of snake antivenoms. Early reactions can be classified as: 1 – Pyrogenic reactions, or 2 – anaphylactic reactions, depending on whether their pathogenesis involves the participation of bacterial endotoxins or the involvement of intrinsic (non-microbial) components, such as immunoglobulins, respectively.

According to clinical studies reported in the literature, most antivenoms induce early reactions in around 20% of the patients. However, there are products with incidence as high as 88%, or as low as 3% of patients (Table 1). There are no clinical studies reporting the absence of early reactions to antivenoms (Table 1). Such high variability in the incidence of early adverse reactions by antivenoms reflects the high heterogeneity in the safety profile of these products.

3.1. Pyrogenic reactions

Pyrogen is a term used to refer to any substance capable of inducing fever. Pyrogenic reactions (characterized by increase in body temperature, rigors, myalgia, headache, nausea, sweating, chills, increase of the heart rate, and vasodilation with secondary fall in blood pressure), occur during the first hour after initiating the administration of an antivenom contaminated with pyrogenic substances. Adrenaline and anti-pyretics are the standard treatments for this type of reaction. Implementation of Good Manufacturing Practices (GMPs) in antivenom production precludes the appearance of pyrogenic reactions by avoiding the contamination with microbial products (WHO, 2010a).

Many substances induce pyrogenic reactions. However, bacterial lipopolysaccharides (LPS) are the most common pyrogens in biologically-derived pharmaceuticals (Magalhães et al., 2007). LPS are integral components of the outer cell membrane of Gram-negative bacteria. They are amphiphilic molecules formed by 1) the hydrophobic lipid A, which is responsible for the biological activity of LPS; 2) the hydrophilic core oligosaccharide, which provides negative charges that affect the biological activity; and 3) the O-antigen, which contributes to the antigenic properties of the molecule (Hodgson, 2006).

During multiplication and death of bacteria, LPS are released to the environment within macromolecular complexes called endotoxins which, in addition of LPS, contain proteins and phospholipids (Hitchcock et al., 1986). In aqueous solutions, endotoxins form very high molecular