Comments to the application for inclusion of equine F(ab’)_2 antivenoms in the WHO model list for essential medicines

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The main concern with this application is that it is too specific for the antivenoms manufactured by Sanofi-Pasteur. If the medicine ‘antivenom’ is going to be introduced in the WHO model for essential medicines, it should be introduced in more general terms, not so limited to the four antivenoms manufactured by one producer. This criticism includes several aspects:

(a) First of all, biochemical, preclinical and clinical studies on antivenoms in the last decade have clearly shown that antivenoms of high efficacy and safety can be made of either fragment F(ab’)_2 or whole IgG molecules, and not only of F(ab’)_2 fragments. Although in the past it was assumed (without adequate proof) that F(ab’)_2 antivenoms had a safer profile than IgG antivenoms, based on the belief that adverse reactions to antivenom administration were due to the presence of Fc fragment in whole equine IgG molecules, such assumption has been mostly rejected in controlled experimental and clinical studies. In vitro studies demonstrated that both F(ab’)_2 and IgG antivenoms activate human complement (León et al., 2001). But the most important evidence against such assumption has come from clinical studies. Otero-Patiño et al. (1998) compared the efficacy and safety of antivenoms made of F(ab’)_2 fragments, manufactured by pepsin digestion of horse IgG and two products made of whole IgG molecules, one of which was prepared by ammonium sulphate fractionation and the other by caprylic acid precipitation. The results of this clinical trial, performed in Colombia, clearly showed that the three antivenoms were effective, and caprylic acid-fractionated whole IgG antivenom induced the lowest incidence of early adverse reactions, followed by the F(ab’)_2 anivenom and then by ammonium sulphate-fractionated whole IgG antivenom which showed the highest incidence of early adverse reactions. In other words, the issue at stake in relation to safety is not whether antivenoms are made of F(ab’)_2 fragments or whole IgG molecules. Instead, the critical issue seems to be the physicochemical quality of antivenoms. Thus, IgG antivenoms made by caprylic acid fractionation yield highly purified IgG preparations of excellent physicochemical qualities.

This alternative interpretation is supported by two types of observations performed in other clinical trials: (i) Various clinical studies with F(ab’)_2 antivenoms of different manufacturers have shown that the incidence of early adverse reactions with these products range between 5% and 85%. Such ample variation can be explained on the grounds that the physicochemical quality of these products (purity of the active ingredient, presence of protein aggregates, and total concentration of equine protein) are highly different among products. (ii) A study that compared two antivenoms made of IgG, one fractionated using ammonium sulphate and the other using caprylic acid, clearly demonstrated that the former induced a significantly higher incidence of adverse reactions than the latter (Otero et al., 1999). Again, the reason behind this observation lies in the fact that IgG antivenoms prepared by ammonium sulphate precipitation contain more protein aggregates, a higher total protein concentration and
a higher proportion of on-IgG serum proteins. Other studies carried out in Colombia and Costa Rica with caprylic acid-fractionated whole IgG antivenoms also demonstrated a low incidence of early adverse reactions, which are mild (Arroyo et al., 1999; Otero et al., 2006). In other words, the issue at stake is not whether antivenoms are made of F(ab')₂ fragments or whole IgG molecules, but instead the issue is the purity and physicochemical quality of the product. Anivenoms with a good efficacy and safety profile could be composed of either F(ab')₂ fragments or whole IgG molecules, provided their physicochemical quality is assured.

(b) From a pharmacokinetic standpoint, antivenoms made of whole IgG molecules or of F(ab')₂ fragments have an adequate profile, especially regarding the neutralization of viperid snake venoms. Both of them have a volume of distribution that exceeds the plasma compartment, thus reflecting their ability to reach the interstitial compartment and, more importantly, both of them have a relatively high elimination half-life, thus remaining in the circulation for many hours. This second point is relevant since it has been proposed that ‘recurrences’ of envenoming occur in viperid snakebites due to late release of venom from tissue depots to the circulation (Gutiérrez et al., 2003). In these circumstances, it is important for an effective antivenom to maintain high concentrations in blood, as do F(ab')₂ and whole IgG antivenoms.

Therefore, there is ample experimental and clinical evidence supporting the concept that effective and safe antivenoms may be composed of either F(ab')₂ fragments or whole IgG molecules, provided the products have a good physicochemical profile. It seems therefore inconvenient to introduce only the F(ab')₂ type of antivenom in the list of essential medecines, since this may limit the use of whole IgG antivenoms which, when properly manufactured, have proven highly effective and safe.

(c) An additional point of concern with this application is that it refers only to four very specific types of antivenoms manufactured by a single producer. Thus, the scope of venoms neutralized are limited and do not cover venoms from the Americas, for instance. It seems more appropriate to present the medecine ‘antivenom’ in more general terms, emphasizing that antivenoms should be able to neutralize a minimum number of LD₅₀s of the venoms against which the product is manufactured, without specifying which venoms are neutralized.

In conclusion, it is suggested that if the medecine ‘antivenom’ is going to be placed in the list of essential medecines of WHO, the description of the medecine should be made in more inclusive terms, allowing both F(ab')₂ fragment antivenoms (prepared by the methodology described in this application) and whole IgG antivenoms (prepared by caprylic acid fractionation of plasma). In addition, the description of the venoms being neutralized by the products should not be too specific, and the possibility of other products, of varying specificity, should be left open.
References cited


