



BLOOD PRODUCTS ADVISORY COMMITTEE

83rd Meeting - July 21, 2005

Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, MD 20877

Topic III: Prophylaxis of Dextran-Induced Anaphylactoid Reactions (DIAR) by Dextran 1 Pre-Administration

ISSUE:

The FDA seeks advice from the Committee regarding informing the medical community of the risk of dextran-induced anaphylactoid reactions (DIAR) associated with the use of Dextran 40 and Dextran 70 and the benefit of prophylaxis with Dextran 1.

BACKGROUND:

Two intravenous dextran solutions, Dextran 40 and Dextran 70, have been marketed in the U.S. for more than 40 years. They are approved for plasma volume expansion in the treatment of hypovolemic shock, as a component of the pump prime for cardiopulmonary bypass, and for postoperative thromboembolic prophylaxis. Because they reduce platelet aggregation and promote blood flow in the microcirculation, dextran solutions are commonly used by plastic and ENT surgeons for patients undergoing plastic reconstruction skin flaps and by vascular surgeons for patients undergoing carotid endarterectomy.

The occurrence of dextran-induced anaphylactoid reactions (DIAR) ranging in severity from mild erythema (Grade I) to mild hypotension (Grade II), severe hypotension and bronchospasm (Grade III), cardiorespiratory arrest (Grade IV), and death (Grade V) have been well recognized since the 1960s. Grade III-V reactions are initiated by cross-linking of dextran-specific IgG with dextran molecules; binding of IgG complexes to receptors located on the membrane surface of mast cells and basophils triggers them to release potent vasoactive mediators that cause circulatory collapse and severe bronchoconstriction. The mechanism(s) underlying Grade I and II reactions is (are) not clear.

In the early 1970s, researchers studying a canine model of DIAR discovered that administration of haptan, Dextran 1 (molecular weight 1000), immediately before administration of Dextran 40, greatly reduced the incidence of severe hypotension.¹ Shortly thereafter, a series of prospective, very large (N=76,290), multicenter clinical trials were undertaken in Scandinavia that compared the incidence of severe DIAR in Dextran 40/Dextran 70 subjects receiving Dextran 1 versus the incidence of severe DIAR in a pre-Dextran 1 era, historical control cohort;²⁻⁴ individuals in the control cohort came from the same Swedish, Finnish, and Norwegian hospitals as in the prospective trials.⁵ These studies reported that pre-injecting 20 mL Dextran 1 reduced the incidence of severe DIAR from a control event rate of 25 cases/100,000 units Dextran 40/Dextran 70 to 3/100,000 units. Publication of these findings soon led to licensure of Dextran 1 in Sweden and other countries, e.g., Dextran 1 was approved in the U.S. in 1984. The labeled indication for Dextran 1 is for prophylaxis of DIAR. According to a postmarketing surveillance study that compared historical control data with data from dextran manufacturers and from the World Health Organization database INTDIS for the period 1983-1992, introduction of Dextran 1 into clinical practice was associated with a 35-fold reduction in the incidence of severe DIAR and a 90-fold reduction in the incidence of lethal DIAR.⁶

DISCUSSION:

Three manufacturers currently market Dextran 40 and/or Dextran 70 in the U.S.: Baxter, B. Braun, and Hospira; the only manufacturer of Dextran 1 is Meda AB. FDA review and evaluation of the labeling for the Dextran 40 and 70 products revealed that the recommendation to pre-inject Dextran 1 to reduce the incidence of severe DIAR was present in the labeling of the first Dextran 40 product marketed in the U.S. (by Pharmacia), but NOT in the labeling of products marketed subsequently by Baxter, B. Braun, and Hospira. Our review of the Adverse Events Reporting System (AERS) database showed that 90 cases of severe DIAR had been reported for the period 1969-2004. For most of the reported cases, we do not know whether or not the patients were pretreated with Dextran 1. Since AERS is a passive reporting system, the actual incidence of severe DIAR is likely to be higher, especially since Dextran 40 and Dextran 70 have been approved for decades. Based on our review of the published literature and on reports received in the AERS safety database, we believe that steps should be taken to better inform the medical community regarding the risk of DIAR associated with the use of Dextran 40 and Dextran 70, and the benefit of prophylaxis with Dextran 1. Towards that end, we have engaged the product manufacturers in a dialogue to discuss their findings and interpretations regarding this safety issue and to solicit proposals for dissemination of appropriate medical information. We will invite the manufacturers to present their perspectives and proposals at the BPAC meeting, and we will entertain a discussion on the most appropriate response to this concern.

QUESTIONS FOR THE COMMITTEE:

Please discuss what revisions to the product labeling for Dextran 40 and Dextran 70 would be most appropriate to address the risk of DIAR and the relevance of pre-treatment with Dextran 1. In particular, please comment

- a. whether a class labeling change is warranted, and
- b. what other forms of risk communication FDA should consider to alert the medical community about the risk of DIAR.

REFERENCES:

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