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Assessment of dextran antigenicity of intravenous iron products by an immunodiffusion assay
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LETTER

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Sir,

We have read the article by Susann Neiser *et al*. in a previous issue of this journal 2011;25(3):219-224 with the title: "Assessment of dextran antigenicity of intravenous iron products by an immunodiffusion assay" and feel motivated to comment on it critically since we feel that the methodology and conclusions contain some errors which fundamentally challenge the interpretation of the findings.

The clinical relevance: The assessment of the antigenicity of an injectable molecule for the human organism requires human patient sera due to the inherent variability of antibodies from person to person, and the inherent variation of bioactivity of antibodies within a single individual. Antibodies produced experimentally in animals give little information with regard to clinical effects of the antigenic structure.

The authors postulate in their conclusion that "the reported immunoassay represents a possible approach for the evaluation of the risk of DIAR (dextran induced anaphylactic reactions)". Dextran reactive antibodies have been intensively investigated in the past due to rare allergic reactions to large doses of high molecular weight dextrans used as plasma expanders[1-5]. These studies showed that the vast majority of normal volunteers have detectable levels of anti-dextran antibodies in their blood, yet the risk of clinically significant anaphylactoid reactions is well below 0.1%. Although some degree of correlation was found between the antibody titre (i.e. concentration) and the risk of anaphylaxis among patients exposed to dextran infusions, it was however concluded that "dextran reactive antibodies per se have no pathogenic importance, since the great majority of volunteers with dextran reactive antibodies tolerate high molecular weight dextran infusion[6]. The true biological mechanism of dextran related anaphylaxis is explained as immunocomplex anaphylaxis with some still unknown aspects.

The antibodies used: The authors postulate that antibodies prepared under highly artificial conditions in experimental animals can be used to predict the risk of clinical allergic reactions in patients. It is well known

from any textbook of immunology that experimental immunisation using standard adjuvants is the standard procedure of today, to provoke antibody reactions that would not otherwise occur without such artificial procedure[7]. To further underline the inappropriateness of the present article, the methodology section does not contain any information on the antibody specificity or immunisation procedure used, which also raises questions, since all data in the article is based on this one experimental antibody.

The methodology used: The authors apply the radial immunodiffusion technology for the investigation of immune reactions between IV iron compounds and the experimental antibody. This technology from the 1970s is rarely used today due to its low sensitivity. Analytical techniques for precise characterisation of anti-drug antibodies (ADAs) have developed considerably over the last few decades due to the need to measure neutralising antibodies to widely used genetically engineered protein drugs such as insulin or the TNF-α inhibitors[8]. The frequent occurrence of anti-TNF-α inhibitor antibodies in patients does not generally lead to anaphylactic events, but may result in rapid removal of the drug from the circulation resulting in reduced half-life, reduced bioactivity and reduced clinical efficacy[9]. Today's standards for analysis of ADAs are highly sensitive radio-immunoassays (RIAs) or highly sensitive enzyme linked immune-sorbent assays (ELISAs) which also enable analytical detection of subtype specific antibodies.

It is regrettable that the authors have chosen an almost obsolete methodology and that the experimental setup is lacking proper controls which makes it difficult or impossible to judge the significance of the very faint precipitation patterns observed. It is thus not possible from the hardly visible precipitations to conclude whether they represent artefacts or true reactions. Under normal circumstances it is also required that precipitation rings in immunodiffusion analysis are clearly separated from the application well in order to be judged a positive reaction. This requirement is unfortunately not fulfilled in the present publication.

Bioactivity of antibodies: It is well known from any textbook of basic immunology[7] that the mere presence of antibodies does not imply a particular pathogenic or protective immune reaction or biological activity. The bioactivity of any antibody molecule is variable and linked to the constant part (Fc-fragment) of the antibody molecule, which possesses the receptor sites for initiation of bioactivity. This bioactivity may vary from none – if the antibody is responsible for conferring tolerability – to induction of inflammation or anaphylaxis if the antibody molecule has the ability to bind to specific receptors on cell surfaces like high affinity FER on mast cells or basophils or to form antibody-antigen aggregates of sufficient size to activate the complement system or trigger the various other cascades.

The team of authors: All the authors are affiliated to a company (Vifor) producing products competing with dextran-containing products. This may represent a conflict of interest in interpretation of test results.

Conflict of interest statement.

The authors of the letter have no conflict of interests. They are not financially connected with any company possibly involved with the content of either the article in question or this Letter to the Editor.

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