Complement Activation-Related Pseudoallergy

Mechanism of Anaphylactoid Reactions to Radiocontrast Media and Drug Carrier Liposomes and Micelles

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Abstract: There are numerous drug-induced immediate hypersensitivity reactions (HSRs) that do not fit in Gell and Coombs’s Type I category of drug allergies, characterized by a pivotal role of allergen-specific IgE. Such non-IgE-mediated reactions, also referred to as “anaphylactoid, pseudoallergic or idiosyncratic”, are caused, among others, by radiocontrast agents, liposomal drugs and micellar solvent systems containing amphiphilic lipids or synthetic block-copolymers. A common feature of the latter agents is that they activate the complement (C) system, and that the reactions they cause can be explained with anaphylatoxin action. This chapter surveys the experimental and clinical evidence for the involvement of C activation in HSRs caused by agents in the above three categories. Further subjects include a proposal to update the classification of Type I allergy to according to the mechanism of mast cell (and basophil) activation, to direct and receptor-mediated reactions, with the latter category divided to IgE-mediated true allergy, C activation-related pseudoallergy (CARPA) and mixed IgE/C-triggered HSRs. The review also surveys the risk factors, laboratory prediction and pharmacological prevention of CARPA.

Key words: allergy, anaphylatoxins, anaphylactoid reaction; micelles, radiocontrast agents, cancer chemotherapy, Taxol, Cremophor EL

1. INTRODUCTION

It has been estimated that as many as 30% of hospitalized patients may have a drug reaction of some type, with the incidence of severe and fatal reactions being approximately 7% and 0.3 %, respectively (1). These statistics imply roughly 2 million serious reactions per year with ~100,000 fatalities, making adverse drug reactions the fourth to sixth leading cause of death in the USA (1).
Another recent analysis pointed out that about 25% of all adverse drug reactions are of allergic nature (2). These allergic drug reactions were classified by Coombs and Gell in four groups referred to types I to IV (3). Type I reactions were defined as IgE-mediated acute hypersensitivity reactions (HSRs), while the type II-IV categories enclosed those subacute or chronic reactions that are mediated by IgG, immune complexes or lymphocytes, respectively (3). While this categorization certainly accommodated all kinds of HSRs known at the time of its conception, some 60 years ago, recent estimates suggest that the majority of acute HSRs is not IgE mediated, and therefore cannot fit formally in the Type I category. According to Demoly et al. (2) these non-IgE-mediated acute reactions may represent as high as 77% of all immune-mediated immediate HSRs, implying that approximately 20% of all adverse drug reactions, ∼400,000 severe and ∼20,000 fatal reactions each year in the USA (1) are excluded from Coombs and Gell’s classical scheme. The symptoms of these non-IgE-mediated reactions overlap, but at the same time also differ from those mediated by IgE (Table 1).

Table 1. Symptoms of IgE-mediated type I allergy and pseudoallergy

<table>
<thead>
<tr>
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<th>IgE-mediated</th>
<th>Non-IgE-mediated</th>
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<tr>
<td>Common symptoms</td>
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<td>Anaphylactic shock, angioedema, asthma attack, bronchospasm, chest pain, chill, choking, confusion, conjunctivitis, coughing, cyanosis, death, dermatitis, diaphoresis, dyspnoea, edema, erythema, feeling of imminent death, fever, flush, headache, hypertension, hypotension, hypoxemia, low back pain, lumbar pain, metabolic acidosis, nausea, pruritus, rash, rhinitis, skin eruptions, sneezing, tachypnea, tingling sensations, urticaria, wheezing</td>
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<tr>
<td>Unique symptoms</td>
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<td>- Reaction arises after repeated exposure to the allergen</td>
<td>Reaction arises at first treatment (no prior exposure to allergen)</td>
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<td>- Reaction is stronger upon repeated exposures</td>
<td>Reaction is milder or absent upon repeated exposures</td>
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<td>- Reaction does not cease without treatment</td>
<td>Spontaneous resolution</td>
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<td>- Reaction rate is low (&lt;2%)</td>
<td>High reaction rate (up to 45%), average 7%, severe 2%</td>
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At present most immunology and allergy textbooks refer to non-IgE-mediated HSRs as “anaphylactoid, pseudoallergic or idiosyncratic” without defining their pathomechanism. Thus, reactions caused by radiocontrast media (RCM), nonsteroidal anti-inflammatory drugs, analgetics, morphine, insect venoms, liposomal drugs and many other agents are enlisted within this vaguely defined category. Although the exact underlying mechanism probably differs in each of these drug categories, there is overwhelming