MECHANISMS OF HYPERSENSITIVITY TO INTRAVENOUS AGENTS

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ABSTRACT


Adverse reactions to intravenous anaesthetic drugs and plasma substitutes in man and other mammals exhibit features commonly attributed to immediate Type I immunological hypersensitivity (anaphylaxis). However, the majority of reported reactions have occurred upon first exposure and consequently have little possibility of antibody mediation. In such responders, reactions may re-occur unpredictably with other unrelated substances at a later date. Investigation of the mechanism of reactions becomes essential not only for the individual but also for the evaluation of new intravenous agents.

Several major reaction mechanisms can be demonstrated: IgE and other antibody mediated reactions (the latter involving complement), and non-immune reactions such as direct activation of the C3 alternative pathway and pharmacological reactions in which the drugs cause vasodilation either by direct physiological action or indirectly through the chemical release of vasoactive substances from cells. In mammals other than man, dose-related responses play an important role.

Barbiturate hypnotic drugs produce fewer adverse reactions in all mammals than those which contain Cremophor as a surfactant (e.g., Saffan). Although Althesin (Saffan) reactions are rarely fatal in man, they are predominantly fatal in cats and dogs. This increased risk is associated with the use of this particular surfactant which gives rise to remarkable species difference in adverse response to the same drug. Thus immune reactions to Cremophor or to Althesin may be accurately predicted in the pig following a repeat exposure to the drug, whereas in man repeat exposure may only increase the risk of reaction from 1:10,000 (on first exposure) to 1:1,000 inductions. Cremophor alone causes severe anaphylactoid shock in the dog, limited response in the cat and none in man. These reactions may occur on first exposure and are mediated by direct histamine release.

Unlike anaesthetic drugs, dextran and gelatine plasma substitutes do not release histamine in all species. Even when histamine is released there is a poor correlation with the severity of clinical response.
INTRODUCTION

In 1902 two French scientists, Portier and Richet, found that sublethal quantities of sea anemone toxins injected into previously sensitized dogs caused immediate convulsions and collapse. They proposed the term ‘anaphylaxis’ to describe the phenomenon, as a contra-distinction to the beneficial prophylaxis brought about by vaccination, although even the latter was giving rise to some misgivings. Von Pirquet and Schick, treating a diphtheria epidemic in Vienna with horse antiserum, discovered that a second injection of the antitoxin frequently produced a delayed reaction in the children involving fever and transient arteritis. This response, ‘serum sickness’, is now known to be mediated by circulating immune complexes.

Three important points arise from these early observations:
(1) previous exposure to the antagonist is obligatory,
(2) reactions may be immediate or delayed by several days,
(3) the potential harmful effect of circulating immune complexes.

In 1963 Gell and Coombs produced a classification of immunological events occurring in disease, based on the ‘effector’ mechanism, and the tissue damaging event.

Type I — anaphylactic, reagin antibody (IgE) mediated release of vaso-active amines from mast cells.
Type II — cytotoxic antibody actions on target cells.
Type III — formation of immune complexes with possible tissue damage.
Type IV — delayed, cell (T-lymphocyte) mediated ‘graft rejection’.

All four types may be invoked, to varying degrees, in combating disease or other invasive processes. The exaggeration of one or more of these types leads to immunological hypersensitivity.

ANTIGENIC BEHAVIOUR

Although plasma substitutes (gelatins, dextrans) are potentially antigenic, low molecular weight drugs are, at best, incomplete antigens (haptens). However, if the drug becomes covalently bound to a substrate familiar to the host (e.g. a plasma protein) it changes status from hapten to complete antigen. In vivo this may occur when chemically active metabolites of drugs become bound to host proteins and these may then initiate immune response. Since this does not occur in all subjects, some genetic restraints must also exist.

Although unusual, certain drug formulations may predispose to cell mediated reaction (Type IV) through ‘adjuvant’ action. This is particularly true with the detergent Cremophor EL present in the anaesthetic drug combination alphaxalone/alphadolone (Althesin (veterinary Saffan) and propanidid (Epontol)) (Watkins, 1979; Dye and Watkins, 1980). Repeated exposure over a short time scale in man to either of these drugs increases the possibility of serious anaphylactic response and in the miniature pig this has proved to be a highly reproducible phenomenon (Glen et al., 1979).