REPORT OF A SYMPOSIUM:
ADVERSE RESPONSES TO INTRAVENOUS AGENTS

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An International Symposium on “Adverse Responses to Intravenous Agents” held in Sheffield, July 6–7, 1978 attracted 137 registered participants, not only from a variety of countries, but also established representatives of a number of scientific disciplines. The Symposium, organized jointly by the University of Sheffield Departments of Immunology and Anaesthetics, also coincided with the 150th Anniversary of the founding of the Sheffield Medical School.

Despite the intention of the scientific committee to consider the term “adverse” in its widest context to include all reactions mediated through the i.v. route, for the most part the participants showed a marked preference for “anaphylactoid” phenomena, which prompted a definition of the term anaphylactoid early in the proceedings. It was agreed that the term merely defined clinical manifestations (cutaneous, pulmonary and cardiovascular) which resembled those of immediate, immune-mediated, hypersensitivity reactions. In the absence of suitable laboratory tests (not defined) clinical reactions would not be ascribed to classical hypersensitivity mechanisms and would obviously include those produced pharmacologically by the direct action of the agent(s) on mast cells. The use of the terms histaminoid and allergoid (Lorenz, Marburg) to describe clinical manifestations restricted to the skin was also acceptable to the participants.

The Symposium divided into five broad topics, applied equally to i.v. hypnotic drugs with or without neuromuscular blocking drugs, and to plasma substitutes:
(a) Problems associated with the i.v. administration of the agent.
(b) Frequency of anaphylactoid reaction.
(c) Mechanisms, mediators and predisposing factors.
(d) Animal models to study mechanisms.
(e) Management of anaphylactoid reactions.

PROBLEMS OF I.V. AGENT ADMINISTRATION

In the opening session Woods (Sheffield) described the wide range of adverse clinical responses to i.v. agents, in which hypersensitivity reactions occupy only a small part. He discussed the increasing use of i.v. fluids in the U.K., illustrated by reference to the Sheffield Area and with particular emphasis on the common practice of administering drugs after their addition to i.v. infusion solutions. In addition to the increased risk of microbial contamination and subsequent infection, the practice may give rise to unpredictable therapeutic effects as a result of reactions both between drugs and between drug and infusion vehicle. Such drug interactions were explored in greater detail by Davie (Edinburgh), who described both the action of non-depolarizing muscle relaxants and their antagonism and the drugs which could potentiate the action of the relaxants. Davie made the important point that interactions may involve not only the drug which the anaesthetist prescribes, but also those prescribed for the patient by other doctors, those taken without prescription, and certain foods. He stressed the importance of the preoperative visit by the anaesthetist in relation to these points. Woods discussed the potential hazards from the toxicity of plastics used in the manufacture of infusion apparatus. Although the adverse effects of p.v.c. plasticizer are debatable, an interesting new viewpoint emerged in an open paper session from Portex Ltd, who presented data on the design of a cannula to produce optimum flow characteristics and minimum trauma.

The pharmacokinetic aspects of bolus injection were explored by Tucker (Sheffield), who outlined the factors affecting drug delivery to sites of toxicity. These included injection rate and concentration of bolus, binding and ion-trapping by the lungs, interactions with vascular receptors, and the distribution of drugs to various organs of the body. Many of these factors were equally applicable to continuous infusion techniques. Rate of injection proved, as usual, a topic for lively debate with potentially misleading statements from participants that countries using
continuous infusion techniques for hypnotics rarely experience cases of systemic anaphylactoid response. There are, of course, no figures to back these statements. Nevertheless, continuous perfusion techniques with smaller doses and controlled depth of anaesthesia have obvious merit and two papers explored the use of etomidate and Althesin in this connection. Savege (London) reported upon the use of the cerebral function monitor (CFM) to measure the level of cortical activity. He commented on variations in patients of the level of anaesthesia; it is desirable to monitor the level of cerebral depression. The characteristic CFM patterns of change seen with Althesin are mirrored by the barbiturates and although there are limitations to CFM at present, this does seem to be a practical method of monitoring.

Whitwam (London) presented a review of i.v. induction agents, their different properties and side-effects. The last was considered in relation to induction complications, tissue damage, duration of action and recovery. In echoing Woods' opening lecture, Whitwam pointed out that the majority of adverse reactions to these drugs are not immunemediated but originate through side-effects, secondary effects or by overdose.

FREQUENCY OF ANAPHYLACTOID REACTION
The definition of frequency implies that the adverse response can be quantitated in some simple and universally adopted manner. That this was not possible was evident from the speakers concerned with both hypnotics and plasma substitutes, alike. It is evident that, particularly for Althesin, much of the variability must lie in what is regarded by the observer as a significant anaphylactoid response. In the discussions following the papers, attempts were made to define response for reporting purposes. While death was an "acceptable" adverse response, at one extreme of the spectrum many anaesthetists were accepting the "Althesin flush" as normal, although the latter might be a harbinger of future problems in a few unlucky individuals.

I.v. hypnotics
The work of Clarke and Dundee (Belfast) has indicated clearly that clinical features of the reaction include skin changes, hypotension, bronchospasm and abdominal symptoms, in that order of frequency. Clarke demonstrated the fallacy of adverse response reporting in the absence of a measure of severity. In spite of some 90 reactions to Althesin reported in the literature, only one death has occurred and this cannot be attributed directly to the drug. In contrast, there have been six deaths in 45 reported reactions following thiopentone. The data can be interpreted to indicate that, although the patient is more likely to have a reaction to Althesin than to thiopentone, any reaction to the former is unlikely to be fatal. Watkins confirmed the greater frequency of reactions to Althesin than to thiopentone, based on laboratory measurements (62 : 10) and that death was confined to patients other than those receiving Althesin. Fisher (Australia) considered a general frequency of 1 in 5000 for i.v. hypnotics, with evidence of an increasing frequency attributed to cross-sensitivity and the greater number of drugs used per anaesthetic.

Contrast media
Grainger (Sheffield) reported on reactions to intravascular radiological contrast media, essentially tri-iodo-substituted derivatives of benzoic acid. The injected load (perhaps 140 g injected intravascularly within 30 min) is obviously more compatible with the plasma substitutes than with i.v. hypnotic administration. The high dose causes a series of adverse reactions, predominantly because of the osmolarity of the injected solution (five to eight times that of plasma). Anaphylactoid reactions occur also. Mild reactions occur in 1 in 2000 administrations, severe reactions 1 in 20 000 and fatal reactions, 1 in 40 000 administrations.

Plasma substitutes
Plasma substitutes include plasma protein preparations, modified gelatins, dextrans and starches. Anaphylactoid manifestations resemble those of the i.v. hypnotic agents with cutaneous effects, bronchospasm and hypotension as predominant features. Richter (Uppsala) and his colleagues reported data from a recent multicentre prospective study which indicated a frequency of anaphylactoid reactions of 1 in 10 000 for plasma protein preparations, 1 in 1000 for gelatin, 3 in 10 000 for dextran and 8 in 10 000 for hydroxyethyl starch.

MECHANISMS, MEDIATORS AND PREDISPOSING FACTORS
Immunopathological features of anaphylactoid reaction were reported by Glynn, who considered response under two headings, local and systemic. The local reaction is typical of the weal and flare type and was relevant to the histaminoid type of reaction. Glynn went on to describe blister experiments carried out several years ago in children with rheumatic fever. These experiments showed marked
produced convincing evidence for the involvement of patients reacting to all types of plasma substitutes. soluble aggregates or soluble immune complexes in the Uppsala group (Richter, Messmer, Hedin and Ring) predominant mechanisms of response differed. The plasma substitutes, it would not be surprising if the reactions produced both by the hypnotics and by right. Despite the clinical similarity of adverse are potentially antigenic compounds in their own drugs, which are haptenic at best, plasma substitutes thus capable of "tailoring" to suit short- or long-term plasma expansion requirements by varying molecular weight and degree of hydroxyethylation (Mishler, Oxford).

**Mediators**

Lorenz (Marburg) and Doenicke (Munich) pointed out that, at present, it is only possible to define clinical adverse reactions as histamine mediated or non-histamine mediated. There is insufficient evidence to implicate the other putative mediators such as anaphylatoxins, serotin, kinins, prostaglandins and SRS-A. These workers have defined meticulously both the methodology and the criteria for significant histamine release under control and under clinical conditions. Histamine release occurs both in subclinical and in clinically significant cases. In prospective controlled clinical trials in healthy subjects histamine release was demonstrated following thiopentone, methohexitone, propanidid, Althesin and flunitrazepam, but not following etomidate. However, neuromuscular blocking drugs in combination with etomidate also released histamine. The plasma expanders, haemaccel, dextran, oxypolygelatin and hydroxyethyl starch, released histamine. Lorenz and Doenicke pointed out not only the direct harmful effects of histamine release in man, but also the importance of showing involvement in clinical and subclinical reactions as a pointer to the possible mechanisms which led to its release.

Unlike histamine, the role of prostaglandins in the anaphylactoid response remains putative. There is evidence to show that prostaglandins may modulate mast cell histamine secretion by interference with variation in blister volume with the stage of the disease, and this was not a permeability effect. It was felt that these experiments might be reviewed with advantage in light of the intradermal testing data supplied by Fisher. Regarding the systemic response, Glynn made important points regarding not only the intensity of reaction but also the susceptibility of different tissues to histamine liberated during the reaction. The "shock organ" shows marked variation between species and probably some variation between individuals within species. This point was echoed later by Pavek (Uppsala), with his cardiac studies.

Watkins pointed out that simple laboratory tests considered in relation to the clinical features of the case afford a useful tool in distinguishing the mechanisms of the adverse response and were essential if investigations into predisposing factors were to be of any value. Few anaphylactoid reactions were immunemediated immediate hypersensitivity reactions (Whitwam). When the latter occur the consequences are likely to be serious. This was in agreement with the nature of reactions to thiopentone (Clarke). Several mechanisms may be involved, irrespective of the type of i.v. agent. Complement C3 activation (alternate pathway) appears to be a predominant feature of reactions to i.v. hypnotic drugs and to radio contrast media (Thompson, Birmingham), but not to plasma substitutes (Hedin, Uppsala). Many reactions may involve a degree of immune recognition involving antibodies other than IgE with subsequent excessive activation of complement. Complement C2 activation caused angio-neurotic oedema without C3 intervention and may indicate genetically prone individuals. Pharmacological or chemically mediated reactions mimic hypersensitivity reactions by release of vasoactive substances, but may be distinguished by consideration of case history, lack of IgE or other antibody involvement, and lack of complement involvement.

**Mechanisms specific to plasma substitutes**

Unlike the hypnotic and myoneural blocking drugs, which are haptenic at best, plasma substitutes are potentially antigenic compounds in their own right. Despite the clinical similarity of adverse reactions produced both by the hypnotics and by plasma substitutes, it would not be surprising if the predominant mechanisms of response differed. The Uppsala group (Richter, Messmer, Hedin and Ring) produced convincing evidence for the involvement of soluble aggregates or soluble immune complexes in patients reacting to all types of plasma substitutes. Among plasma protein solutions HSA is employed most widely. Here, aggregates may form as a result of polymerization upon storage and these may cause early reactions. Late reactions in patients 3 days or more after treatment may represent the immunological consequences of genetic polymorphism. Dextrans and gelatins may react with antibodies already present in the plasma of many patients. Despite their apparent involvement in adverse clinical reactions, the activation pathway of these complexes remains far from clear, although complement C3 activation did not appear to be a specific factor. In this connection, Lorenz and Watkins pointed out that they, too, had not observed C3 activation in cutaneous reactions to dextran, although Watkins reported excessive activation, in two fatal reactions, to dextran.

Hydroxyethyl starch appears to be relatively non-immunogenic. Additionally, the molecule is uniquely capable of "tailoring" to suit short- or long-term plasma expansion requirements by varying molecular weight and degree of hydroxyethylation (Mishler, Oxford).
cyclic AMP production. Although there is little evidence to implicate prostaglandins directly in anaphylactoid reactions, Atkins (Sheffield) pointed out that, since there was a group of asthmatic subjects in whom the disease was exacerbated by aspirin or indomethacin (potent inhibitors of prostaglandin biosynthesis), by analogy some anaphylactoid reactions might occur more readily in patients receiving this type of therapy. He suggested also that Althesin might produce some reactions through steroid inhibition of prostaglandin biosynthesis.

**PREDISPOISING FACTORS**

These factors may be in the injected solution or in the patient. The former are now being investigated by the pharmaceutical industry. It is not yet known what features of anaesthetic drugs predispose to "hypersensitivity reactions". However, the presence of Cremophor EL was considered to be relevant to the high frequency of reactions to propanidid, Althesin and certain preparations of diazepam (Watkins, Clarke, Glen).

There is increasing information about the structure—toxicity relationships in plasma substitutes. Preformed antibodies exist to both gelatins and dextrans in normal individuals and the high frequency of reactions, particularly with the former group, is probably related to this. With the dextrans, the frequency of reactions is related directly to the molecular weight, but it is specific immune complexes of large size rather than the dextran molecule itself that trigger a reaction.

**Patient factors**

There was no evidence that a particular sex or age group was more likely to produce anaphylactoid reactions, although one would expect sensitization of the population in general to increase with age. On the other hand, the severity of reactions and likelihood of fatality, both with i.v. anaesthetics and plasma substitutes, did increase in the older age groups.

A history of atopy (asthma, hay fever or eczema) was significantly more common in patients reacting to various i.v. anaesthetics and plasma substitutes, did increase in the older age groups.

A history of atopy (asthma, hay fever or eczema) was significantly more common in patients reacting to various i.v. anaesthetics than in controls—14% compared with 8.5% (Fee, Belfast). This had been shown by taking as a control-series 10 000 unselected patients in surgical wards who were about to undergo surgery. More specifically, Fisher showed that bronchospasm during induction was more common in patients with a history of asthma. There was general agreement that patients with a history of drug or food allergies were more liable to have reactions to i.v. anaesthetics. The frequency of allergic history was 29% in patients who had experienced anaphylactoid reactions, compared with 13.5% in the general surgical population.

Previous exposure to the same anaesthetic substance was an important predisposing factor, especially in the case of reactions to Althesin (Fee). Watkins and Allen produced evidence for a short-term memory phenomenon in this group of reactions, with a high risk period 1–4 weeks after the first exposure.

Reactions to plasma substitutes occur more frequently in patients with an allergic disposition or auto-immune disease and this correlation was particularly marked in reactions to human albumin rather than dextran (Richter, Uppsala).

Patients with a history of allergy, asthma or previous adverse reaction are three to four times more likely to suffer a severe reaction to contrast media than those without such a history (Grainger).

**Stress**

Anaesthesia and surgery combine to produce marked alterations in hormone concentrations in the patient, mediated through various centres in the brain. This causes specific changes in plasma chemistry, cell metabolism and various immunological indices. The last are of particular interest and potential importance. Walton (London) reviewed the literature. Both cellular and humoral limbs of specific immunity are affected after operation by anaesthesia and surgery. The overall findings are of depression of immune competence as measured in vitro. However, the latter must be viewed with caution, since the lymphocyte transformation and leucocyte migration tests currently employed for this purpose are extremely crude and merely express in vitro sensitivity of cells to particular agents. Any extrapolation to the patient must be made with extreme caution (Glynn), particularly since there are specific problems with testing leucocytes exposed to hypnotic drugs (Watkins). Nevertheless, it must be accepted that immunosuppression after surgery will have implications for increased susceptibility to infection and, more important, to loss of immunological control of micro-metastases in the surgically treated patient with cancer.

**ANIMAL MODELS**

Elimination of adverse reaction potential in new products would be helped greatly if there were suitable animal models and, as in the field of malignant hyperthermia, the pig has proved to have a high susceptibility. Davies and Glen (I.C.I.) have investi-
gated a range of anaesthetic drugs and solvents on the so-called "mini-pig" and found a frequency of up to 80% with repeat exposures 7 days after the first. Thiopentone and propanidid produced a minimum of abnormalities on any test. However, propanidid and Althesin in the standard solutions and even alphaxalone/alphadolone in organic solvents caused the typical clinical response plus a reduction in polymorph count and an increase in plasma histamine, when given twice with a 7-day interval. It has not yet been shown that these reactions involve the same mechanisms as those in man, nor where the barbiturate reactions fit into the picture, but it appears to be a new and rewarding field for studies in drug toxicity.

The monkey has been investigated for reactions to plasma substitutes (Hedin), but the approach has so far been mainly immunological. It is not yet known whether it will be possible to "screen" plasma substitutes on any type of animal model, not least because of the absence of a trouble-free colloid.

MANAGEMENT OF ANAPHYLACTOID REACTIONS

**Prevention**

These reactions, although increasingly common, were rarely fatal. Reaction liability is not, therefore, the only factor in selecting a particular drug or treatment, although it may discourage the use of Cremophor-based induction agents or the gelatin plasma expanders. Active prevention must depend on two types of drug, disodium chromoglycate and H₁ and H₂ receptor antagonists. The former has not been studied sufficiently in premedication, but it is likely to be effective particularly in preventing bronchospasm in susceptible individuals (Keogh, Fisons). It is of no value in the treatment of established reactions.

Histamine release is a feature of all anaphylactoid reactions and a direct consequence of injections of many anaesthetic drugs. Pretreatment with antihistamines is logical, particularly in susceptible individuals (Lorenz). It is probably important to antagonize both the H₁ and H₂ actions and so far much less is known about the latter aspect. However, studies in human volunteers exposed to haemaccel are promising (Lorenz, Schoning, Heidelberg) and it remains to test the combination on patients. Again, these drugs are of little value in treating the acute established reactions.

Steroids also are included in the list of prophylactic drugs, but with less assurance, and it must be recognized that to give all susceptible individuals this battery of drugs would sooner or later produce its own toxicity.

Fisher emphasized the responsibility of the anaesthetist in identifying the particular drug involved so that the patient may carry a suitable warning. He advocated intradermal testing (which carried a minimal risk if performed properly), by which he had found a high yield of clear-cut results. It had certainly increased our realization of the role of neuromuscular blocking drugs in causing true anaphylactic reactions, and the better known direct histamine liberation. Other speakers were sceptical of the value of these tests, and Watkins continued to press for complement and IgE estimation in the first few hours after a reaction to elucidate its nature and (less reliably) its cause.

**Treatment**

The most common manifestation of an anaphylactic reaction is hypotension, with extravasation of fluid into extracellular tissues. This is mediated by histamine which induces peripheral vasodilatation and venous pooling. The treatment of this is clearly administration of fluid, preferably a colloid plasma expander (Fisher, Pavek). The fluid should be transfused rapidly up to a volume of 1-2 litre, but the volume must be monitored continuously by the central venous pressure. Anaphylactic reactions to plasma substitutes are slow in onset, but usually develop within the 1st hour (Richter). In the event of a reaction, the infusion should probably be changed to a purified human plasma protein fraction, which is the colloid least likely to cause further trouble.

There was less unanimity about which drug to use for the treatment of acute hypotension, but adrenaline was favoured on grounds of certainty of effect and availability. Isoprenaline is effective, but may be undesirable because of pre-existing tachycardia. Alpha-adrenergic stimulators such as metaraminol avoid this problem and, since the hypotension is mainly peripheral, would seem to be indicated specifically (Clarke). However, Whitwam pointed out that these drugs reduced the cell content of cyclic AMP and enhanced mediator release. He felt that angiotension was the drug of choice, on theoretical grounds, but it is not commonly available in the operating theatre.

Bronchospasm is the most life-threatening feature of an anaphylactoid reaction and can only be treated by tracheal intubation and the administration of oxygen, adrenaline and aminophylline. No speaker was enthusiastic about the value of steroids, but all
felt that they should be given to reduce the late effects of the reaction.

CONCLUSIONS

It must be recognized that a proportion of patients having anaphylactoid reactions will die in spite of treatment. These patients may have experienced true anaphylactic reaction. Reactions to Althesin and the plasma substitutes appear to be frequent, but rarely fatal. Those to thiopentone are rare but seem to cause proportionately more deaths. Radiological contrast media have probably the highest potential risk, with a fatality rate of 1 in 40,000 patients injected or about 15 patients in the United Kingdom per year. This puts the problem in perspective for the anaesthetist, for the i.v. anaesthetic is only one of many drugs that can cause anaphylactoid reactions. What was not stressed at the Symposium was that there are many commoner causes of death under anaesthesia.