INVESTIGATION OF ALLERGIC AND HYPERSENSITIVITY REACTIONS TO ANAESTHETIC AGENTS

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Some three million general anaesthetics are administered annually in the United Kingdom, for a variety of surgical procedures. It is inevitable that untoward reactions will occur, but it is the incidence of the reactions which gives cause for concern.

Lunn and Mushin (1982) described almost 300 deaths per year totally attributable to anaesthesia and a much larger number, 1800 deaths, in which anaesthesia may have played some part. Contrary to general opinion, these deaths were not restricted to “high risk” surgical patients and the authors made the unpalatable observation that the majority of the deaths are probably avoidable. Clearly, the deaths represent predominantly mistakes or errors of judgement, rather than idiosyncrasy or hypersensitivity, although our laboratory suggests that up to 100 of the 300 directly associated deaths may result from the latter mechanisms (Watkins, 1985a).

A more common problem is that of anaesthetic morbidity, with perhaps 10000 patients per year involved in a variety of clinically significant adverse reactions, usually manifest immediately after the induction of anaesthesia and with the general characteristics of immune hypersensitivity reactions. These reactions are in fact characteristic of the i.v. administration of any substance, not simply of anaesthetic drugs, and similar reactions are encountered to plasma substitutes and to the growing use of radiocontrast substances. The reactions may range from relatively minor systemic effects, notably flushing and minor degrees of hypotension (which may not even interrupt the surgical procedure), to varying degrees of brain damage following cardiac arrest. All these patients pose problems for the future and an enormous drain on resources, in time spent in intensive care and repeat surgical procedures.

Limitations of clinical observation alone

The clinical manifestations of these hypersensitivity-like, anaphylactoid, reactions do not reflect the mechanism of the reaction, be it immune (specific to the drug administered) or non-immune (just as likely to occur with entirely different drugs). Indeed, in clinical trials it has proved possible to duplicate the clinical manifestation of minor anaphylactoid reactions simply by the administration of minute amounts of exogenous histamine (Lorenz et al., 1982). While the management of clinically severe anaphylactoid reactions is essentially identical, whatever the cause, future management of the patient, including prophylactic measures, is dependent on a full understanding of the mechanism of the reaction. In a wider context, such investigations should increase our knowledge of the patient likely to be at anaesthetic risk and lead to the synthesis of safer drugs by the pharmaceutical industry.

PRACTICAL METHODS OF INVESTIGATING REACTIONS

Once the anaesthetist has stabilized the patient, thought should be given to investigating the cause of the reaction. If the surgical procedure has been abandoned, a repeat procedure may be required at some early date, posing immediate problems to the anaesthetist in terms of choice of drugs or of techniques. Even in the absence of such urgency, the patient is certainly likely to require further general anaesthetic procedures, throughout life.

No single in vivo or in vitro test will provide the answers: a correct assessment of anaphylactoid reactions requires close co-operation between the anaesthetist involved, the patient, and an experienced clinical immunologist. The aim should be

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to identify the causative drug and the mechanism involved. The latter is probably the most important for the patient’s future care. For example, the characteristics of immune response forecast an enhancement of reaction intensity on further exposure. If in doubt of the causative drug in an established or probable immune situation, the anaesthetist should abandon all drugs used in the previous reactive situation. In practice, a little detective work with the sequence of drug addition and the onset of untoward clinical signs will usually restrict this to elimination only of the drugs used to induce anaesthesia and not those used for premedication. With a non-immune response, substitution of the incriminated drugs with new ones may still generate hazardous situations. In general terms, in the non-immune situation it may be better to contemplate anaesthetic regimens alternative to the i.v. induction route—inhalation induction or regional blockade.

Mechanisms

The principal causes of immediate anaphylactoid shock associated with anaesthesia and surgery are tabulated in table I. While anaphylactoid and anaphylactic mechanisms are equally likely to generate life threatening responses, there is a general feeling that antibody-mediated anaphylaxis is less likely to be reversed, even by prompt treatment of the patient. Diagnosis of anaphylaxis must remain a subjective assessment since, by their very nature, anaphylactoid reactions do not lend themselves to anything but retrospective clinical investigation.

Not all of the mechanisms listed in table I occur with the same frequency and, equally, mechanisms are not mutually exclusive of each other. The majority of reactions, whether ultimately fatal or non-fatal, are likely to represent errors of judgement on the part of the anaesthetist and the surgeon (table I) (cf. Lunn and Mushin, 1982). Genuine drug involved reactions are confined to mechanisms (1) and (2) of the anaphylactic and anaphylactoid mechanisms, respectively (table I). Although true drug specific reactions are confined to anaphylactic, antibody-mediated mechanisms, nevertheless both (1) and (2) of the anaphylactoid mechanisms may still reflect broad class specific features of groups of drugs and other compounds, such as the characteristic molecular groupings common to neuromuscular blocking agents (Assem, 1984) and the chemotoxicity of all radiocontrast materials, reflecting their general properties of hyperosmolarity and hydrophobicity (Bielory and Kaliner, 1985).

<table>
<thead>
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<th>Table I. Classification of mechanisms</th>
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<tr>
<td><strong>Anaphylactoid shock—</strong></td>
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<td><strong>arises from:</strong></td>
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<td>(1) Type I immunological hypersensitivity (antibodies bound to cells; cytotoxic anaphylaxis)</td>
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<td>(2) Anaphylaxis mediated by circulating antibodies (aggregate, immune complex anaphylaxis)</td>
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<td>(3) Drug interactions, and drug overload</td>
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<td>(4) Aggregate (non-immune) anaphylaxis. A further complication of (3) and plasma substitutes</td>
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<td>(5) Unforeseen patient pathology</td>
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<td>(6) Surgical stimulation</td>
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<td>(7) Psychosomatic response</td>
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**Nancy Recommendations**

Guidance on the systematic investigation of anaphylactoid reactions was given at a one-day workshop held in Nancy in March 1982, which brought together anaesthetists and clinical immunologists from Europe to decide upon a standard assessment procedure (Laxenaire, Moneret-Vautrin and Watkins, 1983). Several of the important communications at this meeting were published later in the French literature (Annales Françaises, 1982). It will be helpful to review the original procedure briefly and then draw particular attention to those points which should always be observed, their modifications, and limitations of interpretation. For convenience, the recommendations of the joint anaesthetic and immunological workshop may be considered under three broad headings: (1) Assessment during the anaphylactoid response; (2) assessment 6 weeks later; and (3) communication of the conclusions drawn from (1) and (2).

**Assessment during the anaphylactoid response**

The immediate assessment is concerned primarily with establishing the reaction mechanism. It was recommended that blood samples should be taken into tubes containing ethylenediamine tetracetic acid (EDTA) and into heparin tubes for haematology, immunology, and histamine assay. The first sample should be taken as soon as possible after commencement of the adverse reaction and further samples should then be taken 1, 6, 24 and 72 h after the incident. Routine haematology, including haematocrit, is necessary to ensure correction of plasma protein concentrations for fluid changes brought about both by the reaction itself and from exogenous fluids administered in the management of the reaction. The full differential white cell counts supplied " routinely " from the sophisticated analysers used by modern haematology departments have high precision. This means that even minor shifts in platelet and white cell numbers have high statistical significance, particularly the disappearance of basophils in initial reaction samples, which is highly indicative of a Type I immune response (Theobald-Segalen et al., 1982).

The humoral assessment can include measurement of IgE concentrations, histamine (lithium heparin plasma), and complement concentrations and function.

**IgE concentrations** are readily measured by radioimmunoassay using the PRIST kits sold by Pharmacia (U.K).

**Histamine.** The requirements associated with blood sampling for histamine (Lorenz et al., 1981) effectively preclude this assay from serious reactions. This is particularly unfortunate, since its proven involvement would make H₁- and H₂-antagonism mandatory in the future use for that particular patient.

**Complement assessment** includes the measurement of C3 and C4 and the assessment of the degree of conversion of these proteins. This is achieved by simple immunochemical techniques. In simple terms, involvement of C3 and C4 is likely to implicate an immune reaction, C3 alone a non-immune reaction. The latter implies a broad reactivity to a class of substances, for example radiocontrast substance, or to drugs using Cremophor in their formulation, rather than to a specific drug structure.

**Assessment 6 weeks later**

This is made to diagnose the causative drug(s). The patient is referred to an experienced clinical immunologist. The anaesthetist provides comprehensive details of the adverse incident, a list of all drugs administered and their sequence, a list of previous anaesthetics and the drugs administered (and any untoward sequelae) and any other medical history which may be relevant, including personal or familial traits of allergy or asthma and details of any recent illnesses. The IgE concentrations obtained from the immediate assessment will substantiate any clinical evidence of atopy, particularly if the testing laboratory has screened for specific IgE antibodies to the most common airborne allergens, house dust mite and grass pollens.

All the above are risk factors inherent to the patient at the time of anaphylactoid response. On the basis of this evaluation, and if the findings of the immediate assessment indicate an immune mechanism, then specific antibody response (anaphylaxis) to one or more of the administered anaesthetic drugs may be sought. Three tests were recommended, involving both in vivo and in vitro aspects of immunity:

(a) Skin tests at low dilutions of the drugs (1 in 1000; 1 in 10000).
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(b) Human basophil degranulation test (Benveniste technique).
(c) Antibody passive transfer tests (Prausnitz–Kusner (PK) tests).
Two positive of these three tests would be considered to be a positive identification.

Communication of the conclusions
Results from these tests are then made known to:
(a) The anaesthetist, together with recommendations for future management. If a specific drug response has been identified, then that drug must never be re-administered to the patient and this fact must be entered on his/her hospital records.
(b) The patient. The final procedure recommends that the patient should be given an anaesthetic card with the names of the hazardous drugs entered and that he should carry this at all times.

Limitations in an ideal procedure
The Nancy procedure must represent an ideal, and it would appear to be infrequently achieved, even by our enlightened colleagues in Europe. It can be actually improved by “early” blood sampling during the first 30 min following onset of the reaction, although usually the anaesthetist is far too busy stabilizing his patient to worry overmuch about future anaesthesia! The time sequence indicated was a compromise for the delegates present: the Sheffield Unit prefers immediate (i.e. as soon as possible), 1, 3, 6, 12 and 24 h. Unfortunately, the 72-h sample frequently reflects increases in the acute phase proteins as a result of the body’s stress response to the reaction trauma. A better baseline is achieved several weeks later, even at the 6-week assessment point.

In Sheffield, in order to prevent error by blood samples being inadvertently taken into containers containing the wrong stabilizing agent, we now request only EDTA blood samples, since these are compatible with the requirements for both haematology and serology. Duplicate blood samples should be taken as soon after the procedure (immediate, 1, 3, 6, 12 and 24 h) as convenient to staff and ward schedules.

The use of EDTA confers long term stability of frozen plasma samples over those taken in citrate or heparin, presumably because of the highly effective immobilization of Ca$^{2+}$ ions. It is necessary to use plasma rather than serum to assess both concentrations and function of complement components which are compromised by blood clotting mechanisms. The involvement of both C3 and C4 is highly indicative of an immune reaction which does not involve IgE antibodies. Complement C3 conversion alone (alternative pathway activation) is an indication of a specific non-immune mechanism. The incidence of the latter has declined rapidly with the disappearance of Althesin from the anaesthetic scene, although it is still encountered with radiocontrast media as a predominant mechanism, and sometimes with dextran. Possible angio-oedema traits may be catered for by the assessment of C1 inhibitor concentration in plasma and its function measured in serum. The latter may be made on serum separated from freshly clotted blood taken at any convenient time, after the patient’s recovery.

The complexity of the plasma complement system makes it prone to activation at several points, including inhibition of the normal system “inactivator” enzymes and in response to aggregates of infused molecules resembling immune complexes (for example certain dextrans and albumin preparations).

Involvement of plasma proteins, and particularly complement components, is seen as a reduction, and subsequent recovery, pattern (fig. 1). This reflects their immediate involvement in the reaction mechanism, followed by a very slow replacement, after several hours, from both the extravascular fluid pool and fresh protein synthesis. It is this projection of the reaction, not the reaction itself, which we can follow readily. Proteins may be directly consumed in the reaction, but more often simply “converted” from native molecules into inactive species as a result of the release of their biologically active polypeptide moieties. Until this inactive denatured protein is catabolized, plasma protein concentrations remain almost constant, since the usual immunochemical quantitation techniques make no distinction between native and inactivated protein. Other techniques to demonstrate such changes are necessary and various types of simple immuno-electrophoretic procedures have been described, particularly in relationship to complement components (Watkins, 1982). The term conversion (native to inactive form) is widely used synonymously with native C3 activation by both immune (classic pathway) and non-immune (alternative pathway) mechanisms. However, the other native complement components show conversion, as do
proteins of analogous biological systems such as fibrinogen and plasminogen. The consequences of clinical intervention on the complement system have been reviewed (Watkins, 1985b).

Immunoglobulin IgE frequently shows a reduction and recovery pattern similar to that of complement proteins when involved in reactions (fig. 1). This is particularly evident with increased plasma concentrations (> 100 u. ml⁻¹). This behaviour of IgE response to i.v. therapy is bizarre. The change is too great to indicate specific antibody and again must represent rather drastic equilibration between cell-bound IgE and the circulating material in the vascular and extravascular pools. On the basis of other studies, the author is of the opinion that this pattern of IgE response is consistent with a genuine Type I allergic reaction; he accepts that the view is controversial! Immunoglobulin IgE concentrations around 1000 u. ml⁻¹ and greater are consistent with atopic states and an indication, perhaps, of a patient at risk to multiple i.v. exposure to the same drugs. Assay kits (RAST) to specific anaesthetic drugs are not yet commercially available, although some interest is being expressed by Pharmacia and a working system to a few of the more common drugs is being established (Sheffield—Pharmacia studies).

In contrast to the high-IgE atopy trait, which involves some 10% of the population, interest is gathering in patients with low IgE concentrations ( < 15 u. ml⁻¹) in their plasma. Some 10–20% of the population exhibit such low concentrations. When presenting as surgical patients, these individuals appear both to be prone to non-immune mediated clinical reactions and to produce positive intradermal skin tests with drugs known to have high histamine release potential, particularly neuromuscular drugs (Lavery, Clarke and Watkins, 1985). One hypothesis is that these unfortunate patients respond to drugs administered by the i.v. route simply because their mast cells lack sufficient endogenous IgE to prevent or mask their surface receptors from interacting with these drugs (Watkins, Wild and Clarke, 1985). Further studies are in progress, but we can state that the low IgE concentrations are "inherited", apparently in a manner similar to atopic IgE concentrations, and that the situation is biased towards the female (compare incidence of female reactions to anaesthetics with those in males). It would be advisable to enter this fact upon the patient's notes rather than the negative comment "not consistent with allergy or atopy", since we are not necessarily contemplating an allergic mechanism.

Some type of in vivo assessment is essential and common practice in Europe involves intradermal testing (Fisher, 1979, 1984a). Suitable dilutions of the test drugs (1:1000; 1:10000 and perhaps 1:100000) in saline are injected intradermally (0.1 ml) to the anterior surface of the forearm. It has recently been suggested that this injection volume is too great (Fisher, 1984a) and leads to false positives, but with adequate controls this is really not a problem. Dilute histamine solution is used as a control. A positive result (fig. 2) is a weal at least 1 cm in diameter which lasts for more than 30 min. Unfortunately many drugs, and particularly neuromuscular drugs (e.g. tubocurarine and atracurium), produce an extremely high incidence of false positives (Wood et al., 1985) so that what
is a simple test to perform requires considerable expertise to interpret correctly. The positive artefacts may reflect the pharmacological properties of the drugs and the chemical arrangement of their active groups (Assem, 1984), rather than their immunogenicity. The author prefers scratch or prick tests, the conventional allergen test procedure of the dermatologist. Higher concentrations of the test substances are required (e.g. 1:10). Positive results by this procedure should be accepted as confirmation of a specific drug reaction (fig. 2). Unfortunately, the prick test is rather insensitive and probably misses as many genuine reactions as the intradermal test overestimates. It is strongly recommended that both intradermal and prick tests are carried out simultaneously on the patient’s arms. In the absence of standardized RAST tests to specific anaesthetic drugs, these tests are certainly the best available.

Theoretically, although such tests themselves constitute possible patient sensitization and a potential cause of immediate and life-threatening anaphylactic shock, in practice no testing laboratory has ever reported serious responses. Nevertheless, full recovery facilities must be available.

Passive transfer tests find little use in the U.K. The reasons are multiple: a lack of sensitivity and poor negative predictive value, a risk of hepatitis in humans (Prausnitz–Küstner, PK tests) or a need for animal facilities for passive cutaneous anaphylaxis (PCA), or PK tests. The immunological principles behind such assays may be found in any standard immunology textbook.

The Benveniste test (human basophil degranulation test) is not invasive and may be carried out directly on the haematology samples taken at the time of the incident. It concerns the specific activation, and destruction, of blood basophils and as such can be tested for at any convenient time by challenge of the various drugs against the patient’s isolated and basophil-enriched leucocytes (Theobald-Segalen et al., 1982).

RECOMMENDED MINIMUM PROCEDURE

The following are the recommendations of the Sheffield based national adverse anaesthetic reaction advisory service (NAARAS). It cannot be emphasized too strongly that a successful investigation requires the co-operation of all involved: the anaesthetist and possibly the surgeon, the clinical immunologist, the dermatologist or allergologist and finally, but certainly not least, the patient.

Suggested Procedure

Immediate period

(1) As soon as convenient, the anaesthetist takes duplicate 5-ml EDTA blood samples. These immediate samples are followed by further samples taken 1, 3, 6, 12 and 24 h later, or at some convenient approximation of these times.

(2) At some stage after the reaction is under control, the anaesthetist should telephone the referral immunology laboratory, discuss the case briefly and ensure that the correct samples and documentation will be made.

(3) One set of blood samples are analysed at the
base hospital for complete blood profiles, including cell differential counts.

(4) Plasma is separated from the other sets of samples as soon as possible and stored at —20 °C until despatched to the immunology laboratory together with documentation (5).

(5) The anaesthetist provides a full account of the reaction and relevant clinical background. A “yellow card” adverse reaction notification should be sent to the Committee on Safety of Medicines (CSM).

The immunology laboratory

(6) Analyses the plasma sample and interprets the results in terms of the supplied case history.

(7) Arranges skin tests with the dermatology department at some time convenient to everyone, including the patient.

Communication of conclusions

(8) On the basis of the case history and laboratory tests, including the initial haematological profiles, a conclusion is reached regarding both the probable mechanism and the causative agent(s).

(9) These conclusions are communicated in writing to the anaesthetist concerned and to the patient’s own doctor. Safer drug combinations or alternative anaesthetic regimens are suggested.

(10) The situation is explained to the patient, who should be advised at all times to carry some warning of the risk of anaesthetic reaction, together with suggestions for emergency drug combinations and alternative anaesthetic procedures.

CONCLUSIONS

There are numerous reviews in the literature concerning anaesthetic reactions, their frequency, investigation and future prophylaxis. The reader who wishes to pursue this topic in detail is referred to Watkins and Salo (1982), Fisher (1984b) and Sage (1985).

It cannot be stressed too highly that all clinical adverse events in the U.K. must be reported to the CSM via the familiar “yellow card”. In this way, important patterns of drug reactivity emerge. However, such reporting does not help the individual patient and the procedures discussed in this paper should be considered as complementary to such yellow card reporting in providing a diagnosis of mechanism and causative agent in the individual. Even when patients have not been subjected to immediate laboratory investigation, a relatively simple examination of blood serology and skin tests even weeks after the event may still establish useful pointers to their future clinical management.

In the past there has been a tendency to regard adverse reactions, particularly anaphylactoid reactions in anaesthesia, as rare occurrences in high-risk surgical patients. This is far from the case, and this Unit investigates several deaths each year involving minor “routine” surgery in previously healthy young people. In a recent review Chaplin (1986) made the same point in reporting on the growing number of legal actions for deaths under anaesthesia and on the numbers of irreversibly brain-damaged patients in West Germany. The major causes appear to be similar to those reported in the U.K. mortality study by Lunn and Mushin (1982). Nevertheless, many anaesthetic reactions do resemble those produced by immediate hypersensitivity type mechanisms and laboratory analysis is the only way to distinguish avoidable (human error) from unavoidable hypersensitivity response. In fairness, it must be pointed out that many extremely useful drugs have peculiarities which at first sight may seem alarming, for example skin histamine-releasing properties resulting in exaggerated flushing. Subjective individual reporting without laboratory follow-up could well result in the loss of the drug from the market, which would be to no advantage to patients, and ultimately will discourage the development of better and safer drugs by the pharmaceutical industry.

ACKNOWLEDGEMENT

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REFERENCES