

## Editorial III

### Anaphylaxis and anaesthesia—all clear now?

In 2003, the Association of Anaesthetists of Great Britain and Ireland published the second revision of its *Guidelines on the Management of Anaphylaxis*.<sup>1</sup> The model ‘anaphylaxis drill’, which all anaesthetists must know by rote, underlines the critical importance of intravenous epinephrine, given promptly, in saving lives. However, anaphylaxis remains a challenging condition to treat: 10% of anaesthesia-related reactions reported to the UK Medicines Control Agency (MCA) are still fatal.<sup>1</sup> Interestingly, in 6½ years only 361 reactions were reported to them.<sup>1</sup> In contrast, in France, which has a well-established scheme for reporting reactions, 789 patients were recorded in a 2-yr period.<sup>2</sup> Anaesthetists routinely give many potentially causative agents, perhaps too rapidly and in quick succession, and are therefore the medical practitioners most likely to see severe anaphylaxis.

#### What is anaphylaxis?

Most of us understand the pathological process involving the IgE-mediated release of vasoactive substances from mast cells and basophils after exposure to an antigen to which there has been previous exposure and sensitization: this is the type-1, immediate hypersensitivity reaction. The clinical syndrome associated with an anaphylactic reaction is very variable, both in its features and severity. Indeed, the most severe reactions may involve only one system; for example, the asthmatic with bronchospasm. Ten per cent of reactions involve only cardiovascular collapse.<sup>3</sup> An anaphylactoid reaction is clinically indistinguishable but occurs by a different, non-immune mechanism. Regrettably, the legion case reports of severe drug reactions use these terms loosely and interchangeably. This only causes confusion when trying to establish the cause and mechanism of reactions to different drugs. Laxenaire’s group, who are the French experts on anaphylaxis during anaesthesia, have proposed that all reactions should be described as anaphylactoid unless an immune mechanism has been demonstrated.<sup>2</sup> This is an attractive proposition, not least in that it emphasizes the importance to the clinician of proper reporting and investigation.

#### Incidence and causative agents

If we do not have a definition, nor do we know the incidence of anaphylaxis during anaesthesia in the UK. The authors of the Association guidelines speculate that this may be increasing.<sup>1</sup> Several countries now have national systems for the investigation and reporting of reactions. This is much needed here. To know the true incidence, we must know the true number of reactions, the numerator. All reporting systems are voluntary and under-reporting is

thought to be common. Even in France, where a national reporting system was established in 1985, under-reporting is estimated at greater than 30%.<sup>4</sup> We cannot know the numerator unless there is accurate reporting of all reactions, of all severity, and to all drugs. Similarly, we can only estimate the denominator. This has been done from sales figures provided by the pharmaceutical companies, combined with market surveys of anaesthetists. Correction factors have then been applied to allow for the number of vials used per case, to estimate the number of individuals exposed to each drug.<sup>2, 5</sup> This approach has been criticized.<sup>6</sup>

The incidence of anaphylaxis during anaesthesia has been estimated at between 1 in 10 000 and 1 in 20 000<sup>7, 8</sup> and, despite the comments in the latest guidelines, it seems to change little over time. Sixty per cent or more cases are caused by neuromuscular blocking drugs. Around 15% each are due to latex and antibiotics. Reactions to antibiotics have increased eightfold in a little over a decade; this may be due to increased exposure to antibiotics in the community.<sup>2, 9</sup> Colloid solutions may be implicated in 3–4% of cases.<sup>2, 5</sup> However, any number of drugs have been reported to cause reactions, including opioids and amide local anaesthetics, albeit very rarely in the latter case.<sup>2, 5, 10–12</sup> Only the potent inhalation agents appear blame free.

One must also consider intravenous dyes, such as methylene and isosulphan blue, and radiological contrast media, including fluorescein and the non-ionic, low-osmolar compounds.<sup>13</sup> In one series of 2392 patients receiving isosulphan blue, the incidence of allergic reactions was 1.6%. Most were mild and none of the patients had further immunological investigation.<sup>14</sup> The exact nature of all these reactions (anaphylactic or anaphylactoid) is often not clear in the literature. Indeed, much of the evidence is simply anecdotal. Such reactions may be more common than we realize, however, and we must be vigilant, especially as procedures such as sentinel lymph node detection and endovascular aortic aneurysm repair become more common.

Reactions to chlorhexidine have occurred when it has been used as a skin disinfectant before invasive procedures.<sup>15</sup> Most commonly, these occur during urological procedures. They have also occurred during insertion of central venous and epidural catheters by anaesthetists; one must be careful to allow any skin disinfectant to dry completely before starting a procedure. The chlorhexidine coating of certain central venous catheters has also been implicated in such reactions.<sup>16</sup>

#### Neuromuscular blocking drugs

What of rocuronium? Experience with this drug perhaps best illustrates the problems in trying to define the incidence of

anaphylaxis. Norway and Denmark have introduced allergy networks relatively recently. The Norwegian Medicines Agency, after many reports of rocuronium allergy, recommended that it be withdrawn from routine practice and only used where specifically indicated.<sup>17 18</sup> Predictably, this had a deleterious effect on rocuronium sales in that country. In contrast, in Denmark, only one reaction to any neuromuscular blocking drug (cisatracurium) was recorded over a similar period, compared with four to chlorhexidine (all of which were severe and proven anaphylaxis).<sup>19</sup> The incidence of anaphylaxis to rocuronium in Norway may be calculated as 1 in 5000, compared with 1 in 114 000 in the rest of Scandinavia. This 22-fold difference may be entirely due to chance. We are dealing with a small number of occurrences, and would need a very large sample size to estimate accurately the true incidence of anaphylaxis. Fisher and Baldo have calculated that, if the true incidence was 1 in 5000, the sample size would need to be 7 million to have a 95% chance of being within 5% of the true value.<sup>3</sup> Under-reporting of even a single case in too small a sample causes marked underestimation of the incidence: by 50% in a sample of 10 000 where the true incidence is 1 in 5000. If the sample size is increased to 25 000, failure to report a single case would still lead to underestimation of the incidence by 20%.<sup>18</sup>

Is rocuronium a high risk for anaphylaxis? The French experts would say yes.<sup>2</sup> It is worth remembering that these are cases of anaphylaxis proved by testing, as distinct from anaphylactoid reactions. In the French series, atracurium was more likely to have caused anaphylactoid reactions than rocuronium.<sup>2</sup> The Australians and others would disagree, arguing that the increase in anaphylaxis to rocuronium has mirrored sales, the overall incidence of reactions falling slightly.<sup>20 21</sup>

One must also note that there is no international standard in use either for the description or the diagnosis of anaphylactic reactions. In addition, no causative agent may be found in up to one-third of patients presenting with reactions.<sup>2</sup> Furthermore, newer drugs may be more likely to have adverse reactions reported about them than older ones.<sup>22</sup> For instance, there are many case reports of rocuronium reactions but very few of reactions to succinylcholine in the recent literature, yet succinylcholine has long been considered the worst offender amongst neuromuscular blocking drugs. Scientific journal editors do not publish reports of well-known drug reactions, because they are not new information. It is also probable that increased vigilance regarding certain drugs increases reporting. It may be true that anaesthetists are less likely to report those reactions which are accepted as side-effects of certain drugs, such as the histamine release attributed to atracurium and mivacurium.

## Clinical presentation

The clinical features of anaphylactic and anaphylactoid reactions are well described. Anaphylactoid reactions are more likely to involve skin features (94 vs 72%),<sup>2 5</sup> and

anaphylactic reactions may involve only one system; most commonly, this is the cardiovascular system. Anaphylactic reactions seemed, in the French data, to be of greater severity than the anaphylactoid reactions reported.<sup>2</sup> Might this be explained by the difference in incidence of cutaneous signs, which alert clinicians earlier, between the two groups? We know that some anaphylactic reactions are relatively mild and, even without treatment, self-limiting over 20 min. Are we missing the mild cases of anaphylaxis, attributing the fall in blood pressure or mild bronchospasm to our anaesthetic technique? These patients must be investigated, as re-exposure may be catastrophic. This is a weakness of the management of anaphylaxis, certainly in the UK.

Are some individuals more at risk of anaphylaxis? Individuals with a history of atopy, asthma or food allergies appear to be at increased risk of having latex allergy, but possibly not anaphylaxis to neuromuscular blocking drugs.<sup>2</sup> Other series contradict these findings, as does experience with radiographic contrast media, which suggests an increased incidence of an atopic history in such cases.<sup>23</sup> There is certainly evidence that patients on  $\beta$ -blockers and those with asthma suffer more severe reactions.<sup>23 24</sup> These reactions may be refractory to conventional therapy, and alternative drugs, e.g. metaraminol, may be required, albeit only after further increments of epinephrine. Asthmatics are more likely to suffer severe bronchospasm. Interestingly, the Association guidelines also cite neuraxial anaesthesia as contributing to problematic reactions, as these patients have a reduced catecholamine response.<sup>1</sup>

## Investigation

The new guidelines give explicit instruction on how a reaction should be investigated.<sup>1</sup> It is important that mast cell tryptase is measured. This protein is contained specifically within the mast cell. After degranulation, it is thought to reach its peak level in the plasma after approximately 1 h. Serum samples should therefore be taken as soon as practicable after the start of the reaction, after 1 h and 6–24 h later. A serum sample is required and this should be refrigerated, not frozen, if it can be analysed within 48 h.

Further investigation must be done by an experienced allergist. Centres providing this service in the UK are listed in the guidelines. The aim is to identify the causative agent(s); all possible agents are investigated. There is no gold standard investigation, and any testing is meaningless in the absence of an accurate and detailed clinical history. In this regard, combined clinics are preferred, with an allergist and anaesthetist present. These are becoming more common in the UK.

Once again, the literature is confusing, the generic term 'skin testing' often being used without qualification. Skin prick testing is the usual first-line approach. A positive test combined with a proven rise in tryptase is highly suggestive of IgE sensitization. However, false negatives may occur. Intradermal testing (IDT) may then be undertaken and may

be more sensitive. This is an area of controversy, since it has been shown that even very dilute solutions of neuromuscular blocking drugs, namely rocuronium and cisatracurium, can provoke apparently positive reactions to IDT in non-allergic, healthy subjects; there was no evidence of mast cell degranulation in biopsies of the reaction site in these individuals.<sup>25 26</sup> Reactions were shown to occur even at vial dilutions of 1 in 1000; of concern is that, in the French series, serial dilutions of only 1 in 10 were allowed in clinical testing.<sup>2 5</sup> Normal saline, used as a negative control, may provoke an apparently positive response to IDT in a minority of patients. The response to IDT also varies depending on which site (for example, the forearm or back) is used. Thus, the specificity of IDT and occurrence of false positives may be a concern. One could also argue the converse, in that false negatives are avoided; they may still occur, however.<sup>27</sup> The French group also investigated the presence of specific IgE by radioimmunoassay as a confirmatory test.<sup>2</sup> This highlights the need for experts, not amateurs, to perform these investigations. Only they can interpret the results of an appropriate selection of tests, combined with the clinical history.

The basophil cell surface markers CD63 and CD203c are expressed rapidly and with a high degree of specificity after an anaphylactic reaction. CD63 is present in the basophil granule membrane and appears on the plasma surface of the basophil upon activation. CD203c is a transmembrane protein that is up-regulated after exposure to an antigen to which a subject has been sensitized. Investigation of these markers is now possible *in vitro*, using flow cytometry. This may further refine testing to determine the cause of an episode of anaphylaxis.<sup>28–30</sup> Whilst highly specific for immune-mediated reactions, these investigations seem limited by low sensitivity; in the case of CD63, this may be as low as 50%.

## Cross-reactivity

Regardless of the vicissitudes of testing, cross-reactivity is a problem with the neuromuscular blocking drugs. At least 60% of those allergic to one muscle relaxant may react to another.<sup>2 5</sup> Cross-reactivity may occur between benzylisoquinolinium and aminosteroidal agents. Indeed, there are a significant number of reactions to neuromuscular blocking drugs even where there has been no previous exposure, perhaps in as many as 15% of cases.<sup>2</sup> This may be due to environmental exposure to quaternary ammonium groups, which may be found in items such as cosmetics, over-the-counter medication and cleaning products.<sup>31</sup>

## Conclusions

The diagnosis of anaphylaxis is not straightforward: even less so is its differentiation from non-immune (anaphylactoid) reactions. Identification of the cause is difficult and, too often, not done. As anaesthetists, we are likely to be faced with these challenging conditions, albeit infrequently

as individuals. We must be able to treat the acute event. Further, we must know how to investigate and advise our patients after the event. It is, quite rightly, emphasized in the Association guidelines that it is the anaesthetist's responsibility to ensure that this is done. Many countries now have well-organized systems for the reporting and investigation of drug reactions during anaesthesia. It is our responsibility to refer every possible reaction for investigation, in particular the seemingly mild one, such that we may manage our patients properly, divine which agent is responsible, and define more accurately how often reactions occur.<sup>9</sup> Mild reactions may be difficult to distinguish from well-described side-effects of drugs, or anaesthesia *per se*; for example, the transient skin flushing or hypotension seen with mivacurium. However, where doubt exists, it would seem prudent to refer these patients for investigation as subsequent re-exposure may be disastrous.

An increasing number of regional multidisciplinary clinics now exist in the UK and these are listed in the guidelines.<sup>1</sup> Their further development must be encouraged. The requirement for a national system for the reporting and investigation of possible reactions to anaesthetic drugs is now urgent. It would be apposite for the Association of Anaesthetists or The Royal College of Anaesthetists to lead this development. The Medicines and Healthcare Products Regulatory Agency (MHRA) superseded the MCA on April 1, 2003. Should they, in their role as advocates of patient safety, extend their remit to include the investigation of drug reactions occurring in the UK? We suspect so.

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