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Allergic to Anesthetics

THE article by Mertes *et al.*[1] in this issue contributes important new knowledge to the anesthesia community on the epidemiology of perioperative anaphylactoid and anaphylactic (immunologically mediated) reactions in France. Although cutaneous reactions to drugs are common, life-threatening reactions to anesthetic drugs and adjuvants are unusual. These reactions occur approximately once in every 5,000–10,000 anesthetics. Over half of these serious reactions are immunologically mediated; the remainder are chemically mediated. Because most anesthesiologists witness only a few such reactions in a lifetime, mechanistic and epidemiologic studies such as this provide insights that can contribute directly to clinical practice. Mertes *et al.*[1] give clinicians new information about the prevention, recognition, and identification of these life-threatening reactions. Their observations confirm and extend those made by the Nancy group in five previous reports over the past 20 yr.[2–6] Taken as a whole, these six studies document the epidemiology of more than 4,500 life-threatening reactions during anesthesia. This report also documents emerging trends in the reactions, provides objective evidence that their etiology can be detected, and offers associations that can directly improve patient care.

Although muscle relaxants remain the primary etiologic agents of immunologically mediated reactions (58.2%, [n = 306]), emerging trends of relaxant use demonstrate that rocuronium (43.1% [n = 132]) has surpassed succinylcholine (22.6% [n = 69]) as the drug most frequently implicated in these reactions. Mertes *et al.* confirm the frequently observed clinical predominance of such reactions in female subjects, thought to be due to a common epitope relaxants share with many cosmetics.[7,8] Such an explanation is consistent with the observation that many patients manifest an allergic reaction to muscle relaxants on first exposure. Their data also remind us that drugs that do not elicit the chemical release of histamine can and do cause allergic reactions. Latex is the second most frequent cause (16.7% [n = 79]) of reactions, but this has not increased significantly since the last survey. Perhaps because of the growing recognition by clinicians and preoperative screening for patients at risk for this syndrome by the radioallergosorbent test and other methods, the twentyfold increase in latex allergy in the early 1990s seems to have stabilized. As the third most common cause (15%), reactions to antibiotics have increased eightfold since 1989. The etiology of this relative and absolute increase in reactions to antibiotics is unclear, but it may be due to a more widespread use of antibiotics in the community. Reports of reactions to opiates and local anesthetics still remain uncommon, despite their frequent identification as allergens by patients. Given the trend toward polypharmacy and the complexity of the surgical setting, it often takes considerable detective work to identify the responsible agent. In a recently reported case, the aprotinin in fibrin glue was implicated as the cause of a fatal anaphylactic reaction.[9] In other instances, an allergy to latex was apparent only after deflation of the tourniquet or as a component of disinfectant sprays used to sterilize anesthesia and surgical equipment.[10,11] However, that so few cases in this series remain without etiology suggests that the tools for a thorough investigation do exist.

The second contribution of the article by Mertes *et al.* is that it shows clinicians how best to identify the agents responsible for these reactions. Few anesthesiologists or allergists have experience with the methodology for skin testing described in detail by the authors. Further, because of the rapid catabolism of histamine and the technical difficulty in sample acquisition and measurement, histamine levels remain mostly a research rather than clinical tool. However, tryptase levels were significantly elevated in only 10.7% of chemically mediated reactions but in nearly two thirds of immune reactions, which gives clinicians a very practical tool for distinguishing between the two types of reactions. The use of tryptase to distinguish between chemical and immune reactions has been the source of debate in previous articles in ANESTHESIOLOGY. *In vitro* studies have suggested a generalized co-release of tryptase by high doses of chemical-releasing agents such as vancomycin.[12] However, in a clinical study of rapid administration of vancomycin, chemically mediated reactions did not cause tryptase release, although histamine levels increased fortyfold.[13] An Australian epidemiologic study suggested that the presence of an increased tryptase level highly favored an

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immunologic mechanism.[14] The present study settles the issue. It demonstrates a positive predictive value of 92.6% and a negative predictive value of 54.6% for tryptase as an indication of an immunologically mediated event. Therefore, the presence of a normal level does not exclude an immunologic reaction; markedly elevated tryptase levels are not found in almost a third of anaphylactic cases. However, a significantly elevated tryptase level (> 25 μg/l) strongly suggests an allergic mechanism. Although the authors appropriately caution that the diagnosis of anaphylaxis should not rely on a single test, the high positive predictive value of tryptase makes it important both medicolegally and for subsequent patient management. As a practical matter, because tryptase (a large tetrameric enzyme co-released with histamine) has a half-life of several hours and is unusually stable even at room temperature, it is possible to harvest samples during or even after urgent clinical situations.[15] A small number of surgical patients will have marginally elevated tryptase levels, so it is highly desirable for clinicians to collect serial samples over several hours.[16]

Another important observation is that although it may not be possible to distinguish between anaphylactic and anaphylactoid reactions in individual patients, cardiovascular and pulmonary events are more common in immunologically mediated reactions, and cutaneous manifestations are more common in chemically mediated reactions. Thus it is not surprising that immunologically mediated reactions were identified as more severe, although death from intraoperative latex anaphylaxis remains a rare event.

The current study also provides specific guidance for clinicians in managing atopic patients. Virtually one third of the patients seen in our preoperative clinic present with some history of hay fever, rhinitis, asthma, or food or drug allergy. Clinicians have long worried whether such patients are more likely to have an anaphylactic or anaphylactoid reaction during anesthesia. Such a correlation holds true for latex allergy. A history of generalized atopy or specific allergy to certain fruits (*e.g.,* kiwi, avocado, figs) are both recognized as significant risk factors for latex reactions. However, other than for latex, a generalized history of allergy seems to be of little consequence in predisposing to anaphylactic and anaphylactoid reactions to anesthetics. Although this finding was expected,[17–19] Mertes *et al.* furnish objective evidence that a history of generalized allergy need not preclude anesthetic choices. Specifically, clinicians should not be concerned about giving a histamine-releasing drug, such as morphine, to a patient with a generalized history of allergy. On the other hand, because there is significant cross-reactivity (as high as 80%) between anesthetic agents (*e.g.*, relaxants), a patient history of specific allergy to anesthetics *is* a cause for concern. These patients merit a more thorough preoperative evaluation and possible referral to a clinical allergist for skin testing. In urgent circumstances, using an alternate anesthetic technique (*e.g.,* regional anesthesia, avoidance of relaxants) may be the best clinical option. Although pretreatment with H1 or H2 antagonists will markedly attenuate chemically mediated reactions[13] and may even reduce the severity of immunologically mediated reactions,[20] this strategy is not a substitute for a comprehensive evaluation and anesthetic plan.

Mertes *et al.* have done a great service to anesthesiologists and patients by continuing their survey and by careful analysis of the resultant data. Although life-threatening anaphylactic and anaphylactoid reactions are infrequent, they do contribute to patient morbidity and mortality. However, in many instances "allergy to anesthesia" is used as an explanation for poor outcome. In the interest of patient safety, it is important that clinicians identify those patients in whom allergy is the real cause of the event and determine which agents are responsible. The anesthesia community has done well with several other challenges to practice (*e.g.,* malignant hyperthermia, the difficult airway). It is hoped that this and other such studies will afford the basis for continued practice improvements.

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Thoracic Epidural Anesthesia

More than Just Anesthesia/Analgesia

SPLANCHNIC hypoperfusion following low systemic perfusion due to trauma, hemorrhage, or circulatory shock is thought to form part of the host response to these types of injury. At the level of the microcirculation, hypoperfusion may result either from redirection of blood flow away from the splanchnic organs, mediated by increased sympathetic activity, or from impaired blood flow distribution within the microvascular networks. Because splanchnic hypoperfusion is considered to be important in the development of increased mucosal permeability, endotoxemia, and organ failure, the adequacy of gastrointestinal perfusion has become a major concern in high-risk surgical and critically ill patients.[1] The importance of this concept is further emphasized by the observation that gastrointestinal hypoperfusion is also associated with increased mortality rates in such patients.[2,3]

In the current issue of ANESTHESIOLOGY, Adolphs *et al.* report the results of a carefully conducted experimental study on the effects of thoracic epidural block on gut microvascular blood flow in a hemorrhage model in rats.[4] The authors clearly demonstrate that thoracic epidural anesthesia (TEA) protected the gut from decreased microvascular perfusion and from increased leukocyte–endothelium interaction associated with insults due to hemorrhage/retransfusion. With regard to the effect of TEA on microvascular perfusion, most of the benefit was observed in the muscularis layer. Because sympathetic nerve fibers were detected in all layers of the gut except the mucosa, the authors argue that the favorable effects of TEA on the microvascular perfusion of the muscularis layer must be explained primarily by the effects of the sympathetic block.

One important issue in the effect of TEA on splanchnic perfusion is the location of the epidural block. A complete sympathetic block in the splanchnic region is achieved only if the spread of the local anesthetic includes the thoracic sympathetic nerve fibers, which extend from T5 to T10. On the other hand, the epidural blockade of lumbar segments results in increased sympathetic activity in the splanchnic nerves due to a baroreceptor drive.[5]

Others have performed studies in the area. Ai *et al.* measured intramucosal pH in the ileum of rabbits to determine the effects of TEA (catheter tip at T8–10) during progressive hypoxia to an inspired oxygen fraction of 0.1.[6] In their study, TEA slowed the progression of intestinal ischemia during hypoxia and conferred protection against an increase in portal endotoxin concentrations. Meissner *et al.* studied the effects of high thoracic epidural block (T1–5) on splanchnic blood flows using the microsphere technique in dogs.[7] The thoracic block did not alter blood flow to the splanchnic organs in the study, but the splanchnic sympathetic nerves were not included in the epidural block. In another study, by Sielenkämper *et al.*, intravital microscopy was used to measure gut mucosal blood flow in the ileum of rats during TEA (catheter tip at T7–9).[8] It was found that TEA increased mucosal blood flow and reduced irregular flow patterns such as stop-and-go flow in the capillary networks of the gut mucosa.

There is some supporting clinical information. In two studies, the effects of TEA in patients undergoing major abdominal surgery were determined using gastric tonometry.[9,10] Both studies found that TEA prevented a decrease in intramucosal pH during surgery; however, in one study the exact location of the epidural block was not given.[9] Mallinder *et al.* studied the effect of TEA (block T5–T11) on gastrointestinal blood flow in patients undergoing colorectal surgery.[11] These authors

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