From the Laboratory to the Bedside

Searching for an Understanding of Anaphylaxis

ALTHOUGH more than 100 yr have passed since anaphylaxis was first reported,1 clinicians continue to struggle with the definition and management of anaphylaxis.2 In a recent symposium organized by the National Institute of Allergy and Infectious Diseases (Bethesda, Maryland) and the Food Allergy and Anaphylaxis Network (Fairfax, Virginia), with representatives from the Center for Disease Control and Prevention (Atlanta, Georgia), the U.S. Food and Drug Administration (Rockville, Maryland), and five different medical specialties including anesthesiology, guidelines were elaborated to clarify the prevalence, diagnosis, and management of anaphylaxis.3 Another goal of this symposium was to discuss research objectives including molecular, immunologic, and physiologic mechanisms responsible for anaphylaxis. In this issue of ANESTHESIOLOGY, Dewachter et al.3 present an elegant Laboratory Investigation that helps to elucidate the pathophysiology of anaphylaxis during anesthesia and illustrates why timely diagnosis and management are essential to prevent rapid cell and organ dysfunction.

The diagnosis of anaphylaxis during anesthesia is difficult. The incidence varies from 1:3,500 to 1:20,000, and many anesthesiologists are never exposed to an episode.4 Cutaneous manifestations are difficult to recognize because most of the body is covered with drapes, respiratory signs are often blunted by the bronchodilatory properties of inhalation anesthetics, and pharmacologically induced hypotension is common. As a result, the diagnosis is often delayed or missed unless severe bronchospasm or arterial hypotension occur.

Although severe cardiovascular collapse occurs during anaphylaxis and is treated with epinephrine, its pathophysiology is not clear. Dewachter et al.3 address this issue by comparing severely decreased arterial blood pressure induced in Brown Norway anesthetized rats with nicardipine or with ovalbumin-induced anaphylactic shock. The time course and the magnitude of the hypotension were similar between the two groups. The skeletal muscle blood flow decreased in both groups after 20–40 min. Evidence of skeletal muscle vasoconstriction in the anaphylactic shock group was further supported by the higher plasma epinephrine and norepinephrine concentrations and the greater gradient between plasma and interstitial epinephrine, compared with pharmacology-induced hypotension. Anaphylactic shock was characterized by a more rapid decrease in tissue oxygen partial pressure values, a rapid and larger increase in interstitial lactate concentrations, and a decrease in interstitial pyruvate concentrations. The end result was a significant increase in the lactate-to-pyruvate ratio, a result not present in the nicardipine group. The authors conclude that the cellular oxygen consumption and metabolic failure present in anaphylaxis may lead to end organ dysfunction and a more difficult restoration of normal homeostasis.5

Although any α agonist would increase blood pressure, the unique pharmacologic properties of epinephrine make it the first-line agent for treatment of anaphylactic shock. Epinephrine, the most potent activator of α-adrenergic receptors, also stimulates β1 and β2 receptors. Incremental doses of epinephrine lead first to stimulation of β2 receptors followed by β1 and α-adrenergic receptors. This is important in the setting of the findings of Dewachter et al.,3 where cardiac function was preserved in the early stages of anaphylaxis. β2-Receptor effects lead to bronchodilation and the increased production of cyclic adenosine monophosphate.5 The importance of the latter property is often overlooked when another α-agonist agent is chosen for the treatment of anaphylaxis. An allergic reaction, as opposed to a side effect, is not dose related; therefore, discontinuation of the triggering agent may not be at all helpful. In contrast, cyclic adenosine monophosphate is helpful because it decreases mediator release from tissue mast cells and peripheral blood basophils. The increases in heart rate and cardiac output that characterize higher doses of epinephrine are likely to compensate for the profound vasodilation, increased vascular permeability, and relative hypovolemia that occur later in anaphylaxis.6

Even if given promptly, epinephrine alone may not be sufficient for the treatment of severe anaphylactic shock.7 The cardiovascular effects of a continuous infusion of epinephrine are more pronounced than with an intravenous bolus injection.8 However, boluses can rapidly achieve high epinephrine concentrations and stop mast cell mediator release.9 Studies support the use of pure α-adrenergic agents such as methoxamine10 and metaraminol11 for the treatment of anaphylaxis refractory to epinephrine. Interestingly, α1-adrenergic stimulation

causes a decrease in tissue concentrations of cyclic adenosine monophosphate, a condition that can enhance the release of mediators from tissue mast cells and peripheral blood basophils.

Other forms of distributive shock (e.g., septic shock) are characterized by the redistribution of blood flow to major organ systems but lack cellular oxygen consumption. Although sepsis is not associated with tissue hypoxia, cellular utilization of oxygen is impaired after septic shock. The role of inflammation in septic shock is well established, and treatment strategies that down-regulate proinflammatory cytokines have been successfully. Furthermore, pentoxifylline, a phosphodiesterase inhibitor, has also been shown to down-regulate the inflammatory cytokines tumor necrosis factor α, interleukin (IL)-1β, and IL-6 in sepsis. The proinflammatory response after hemorrhage has also been attenuated by the potent vasodilatory peptide adrenomedullin and adrenomedullin binding protein 1, which down-regulate proinflammatory cytokines and up-regulate antiinflammatory cytokines (IL-10).

Murine models of anaphylaxis demonstrate that mast cell mediators interact with cytokines (IL-4 and IL-13) to increase the severity of anaphylaxis. Two pathways of murine anaphylaxis have been described: one is mediated by immunoglobulin (Ig) E, IgE– receptor, mast cells, and platelet activation factor and is triggered by small quantities of antigens; the other relies on IgG antibodies, low-affinity IgG-γ receptor III, macrophages, and platelet activation factor and is induced by large quantities of antigen. Interferon γ has been demonstrated to block the cytokine-mediated exacerbation that seems to be involved in both pathways of anaphylaxis in mice models. Furthermore, IgG antibody has been demonstrated in vitro to block IgE-mediated anaphylaxis. However, adrenomedullin, despite having been demonstrated to be a potent pulmonary vasodilator and a cyto- kine down-regulator, did not reverse antigen-induced acute bronchoconstriction in guinea pigs. This indicates that the development of bronchospasm in anaphylaxis requires the presence of previous pulmonary inflammation in addition to mediator release. Asthmatic patients are more likely to experience pulmonary manifestations of anaphylaxis after antigen exposure. Furthermore, adrenomedullin binding protein 1 has been shown to enhance adrenomedullin-mediated cyclic adenosine monophosphate accumulation in cultured fibroblasts. Future interventions in the treatment of anaphylaxis may include the use of adrenomedullin binding protein 1 and anti-IgE and IL-4Rα antibodies. Further studies clarifying the role of inflammation and sympathetic nervous system activation may shed additional light on therapeutic options.

The complexity and severity of anaphylaxis is such that no single algorithm can adequately treat all cases. However, Dewachter et al. take us a step further toward understanding the pathophysiology of anaphylaxis during anesthesia and the rationale for aggressive and prompt resuscitation.

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References

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Incisional Sensitivity and Pain Measurements

Dissecting Mechanisms for Postoperative Pain

Incisional pain mechanisms have been studied systematically for the past 10 yr, increasing the interest in the pathophysiology of postoperative pain.\(^1\) In this issue of *Anesthesiology*, Duarte *et al.*\(^2\) rigorously examined responses to mechanical stimuli after an incision on the dorsum of the rat hindquarters. The study contributes to our understanding of incisional pain mechanisms because hairy skin was incised and the manner in which the model was tested was unique.

Postoperative Pain Measurements

In humans, we have used a variety of methods to quantify pain generated by surgery (table 1, left). After abdominal surgery, we typically obtain pain scores at rest, with ambulation and perhaps during cough.\(^3\) The same measurements might apply to patients undergoing thoracic surgery in which the pain during cough has been linked to outcome.\(^4\) After total knee replacement, pain measurements at rest and during flexion are typical, and greater range of motion in the first few days after surgery is associated with greater function weeks later.\(^5\)

A goal of a perioperative analgesic regimen (e.g., continuous femoral nerve blockade) is to achieve a greater degree of flexion with less pain and fewer opioid-related side effects. In clinical studies, under the best circumstances, the measurement is related to outcome for the surgical procedure (e.g., rehabilitation after knee replacement).

Other pain tests have been explored in patients to attempt to understand sensitization and further quantify postoperative pain. One of these tests is punctate secondary hyperalgesia, usually mapped or quantified by a small punctate mechanical stimulus applied outside the area of an incision, e.g., after nephrectomy\(^6\) or colectomy.\(^7\) In some cases, the force required to provoke pain after surgery is quite small, indicating that a touch stimulus has been converted to pain by the surgery.\(^6\) This remote hyperalgesia is secondary because the test site is outside the area injured by the incision, the area of primary hyperalgesia. Central nervous system sensitization causes pain in the secondary zone because the sensory fibers function normally outside the area of injury.\(^8\)

Other methods, in addition to the area of hyperalgesia outside the injury, have been used to quantify postoperative pain. In one study of pediatric patients, the primary punctate force for the abdominal flexion reflex was measured in children after herniorrhaphy.\(^9\) A week force provoked a flexion response after surgery, and the response magnitude was increased as well. Using a different mechanical test after hysterectomy, a blunt probe was applied near or distant to the incision, and the pressure pain threshold that evoked pain was recorded.\(^3\) Again, a widespread area of sensitivity could be measured and this persisted for up to 1 week after surgery. These tests have the advantage in that the stimuli intensity can be quantified. In clinical postoperative studies, analgesics must be available as needed, and therefore, superimposed on pain scales and pain measurements is analgesic consumption, which may confound the detection of a novel treatment. Furthermore, a problem with some evoked pain measures, such as pain during cough, is that there is difficulty standardizing effort.

Table 1. Methods to Measure Pain in Patients after Surgery and Pain-like Responses in Postoperative Models

<table>
<thead>
<tr>
<th>Clinical Postoperative Pain</th>
<th>Postoperative Pain Models</th>
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<tr>
<td>Pain at rest</td>
<td>Heat withdrawal latency</td>
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<tr>
<td>Pain during activities (i.e., ambulation, coughing, flexion/extension of an extremity)</td>
<td>Primary mechanical withdrawal threshold</td>
</tr>
<tr>
<td>Pressure pain threshold</td>
<td>Secondary mechanical withdrawal threshold</td>
</tr>
<tr>
<td>Area of mechanical hyperalgesia</td>
<td>Guarding</td>
</tr>
<tr>
<td>Flexion response to mechanical stimuli</td>
<td>Weight bearing</td>
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<td></td>
<td>General activity</td>
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<td></td>
<td>Conditioned responses</td>
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Postincisional Pain Measurements in Animal Models

Previous studies using incisional pain models (table 1, right) have used nonevoked guarding behavior, punctate mechanical withdrawal threshold, a distant secondary mechanical withdrawal threshold, heat withdrawal latency,\(^10,11\) and weight bearing\(^2,13\) to measure pain-like responses. In addition, locomotor activity, rearing, and conditioned responses have been used after experimental laparotomy.\(^14,15\) The study by Duarte *et al.*\(^2\) examined several new tests for pain after a hairy skin incision (table 2). First, the intensity of the response was measured, rather than an “all-or-none” response. Second, the responses were
separated into alldynic-like and hyperalgesic-like responses based on careful characterization of the stimuli. Finally, in this model, the regions of primary and secondary hypersensitivity are easily distinguished, and these have distinctive time courses and unique responses to treatments. Profound plasticity, an area of intense interest to pain research, is evident in the secondary zone. The precise clinical role of these sensitization phenomena, primary (injured territories) and secondary (uninjured territories) responses, and postincisional hyperalgesia and allodynia, are not yet understood, as noted by the authors.

A challenge for research in postoperative pain mechanisms and for pain research in general is to quantify exaggerated nociceptive responses in both patients and nonhuman models, even though the clinical state, the experimental model, and the tests may not be precisely the same among species. From the preclinical models, mechanisms will be understood, and from the patients, clinical relevance of these tests and treatments that affect the exaggerated processing will be ascertained.

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What’s Wrong with This Label?

I USUALLY listen nightly to 11 min—the monologue—of the Tonight Show while lifting weights. But on Mondays, I listen to a few more minutes of Jay, to hear “The Headlines.” Such “headlines” display newspaper clippings that usually have an ironic twist. For example, last week, the headline above the fold in the Philadelphia paper, “Pennsylvania to Cut School Aid by 80 Million,” was juxtaposed to that below the fold on the same page

the same day, “Pennsylvania Governor Signs Bill to Spend 72 Million to Study Doodle Bug Disappearance.” As I read the article by Chang et al.1 in this issue of Anesthesiology, I smiled to some of the same irony.

Dr. Chang and her colleagues have written a wonderful article giving us meaningful examples of “What’s in a label.” So why the irony? Probably more anesthesiologists will read the article than have read a “label” in the last 5 yr. I would even wager that more doctors have read their palm operating manual than a drug label. What’s wrong with current labels? Why can’t they (whoever they are—more, later) make it simple enough for someone who actually practices medicine, which is bad enough.

References


Table 2. Pain-like Responses after Hairy Skin Incision

<table>
<thead>
<tr>
<th>New Postoperative Pain Models</th>
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<tbody>
<tr>
<td>Primary mechanical allodynia</td>
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<tr>
<td>Secondary mechanical allodynia</td>
<td></td>
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<tr>
<td>Graded hyperalgesia</td>
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<td>Graded allodynia</td>
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This Editorial View accompanies the following article: Chang et al.1 in this issue of Anesthesiology, I smiled to some of the same irony.

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But then, we learn that the drafts of such label are written by pharmaceutical companies who aim to use (read: stay within the legal statements of) the label to market the drug. Some who have read labels might think that pharmaceutical manufacturers are trying to obfuscate information by not making the label readable. Chang et al. state that the goal of the U.S. Food and Drug Administration (FDA) in approving and rewriting such drafts of labels is to provide the information necessary for the practitioner to use the drug for the approved indication in an effective and safe way. Nowhere do they state, or does regulation even imply, that it is to help the practitioner prescribe the drug safely or effectively—only to provide the information. It does not matter that the label is written with so many clauses that many lawyers must be involved and is printed in a font that makes it appropriate only for 18 yr olds with magnifying glasses.

We also learn that the final label involves a give-and-take negotiation between the sponsor (the pharmaceutical company) and the FDA staff—not the doctors of the company and a practicing physician group with the FDA staff overseeing the process. No, it is written, the article by Chang et al. practice indicate, so “safe and effective” seem to be the FDA staff complying with the standard of the regulation and the company having as few restrictions as possible for marketing.

Has the current label pattern ever been tested for facilitating care of a patient? Has it been tested to see whether it might get read and influence practice? Has it been tested against alternatives to determine which might be read more or which might make patient care safer and more effective?

If you have read this far, you probably think I am not likely to be invited by the FDA to be a consultant ever again—but now the attempt at redemption. There should be every reason for a label to be as enticing for physician education as a Glamour cover for attracting female purchasers or as the Sports Illustrated swimsuit issue for attracting male teenagers. The label should compel all to read it so we know more about a drug, not drive us away. And I believe it can be compelling.

Chang et al. also detail the importance, the evolution, and the key components of the label. For those who have not peered at a label recently, they really are more informative than your dad’s label. Many of the labels that were okay only 20 yr ago, when I was first arguing for them to be written better, would never be approved today. (By the way, the ones written 20 yr ago still look the same if the indications for that drug have not changed.) Although it has been an evolving process, it has not evolved in a way that motivates the practitioner to enjoy reading labels (or to read them at all) or makes the practitioner believe that she is helping her patients be safer by reading them. Most of us consider the current label a little less enjoyable than traffic school or as attractive as thrice-reboiled canned peas. And whether I put on my internal medicine hat or my anesthesia hat, the label is still not anyplace near enjoyable, compelling, or user friendly.

The article by Chang et al. should be a wake-up call. The information that they tell us is contained in the label for dosing, duration, side effects, and even chemistry is too important for safe use (patient safety) for it to be written by someone who does not care whether we read it. The article by Chang et al. states that the FDA is considering changing the format of the label—the first ray of hope. Isn’t it about time to reform the label to convey all the information Chang et al. says it conveys in a way that makes us want to read and reread it more than we want to do a crossword puzzle? I hope the FDA takes this as a challenge. Moses found it out: Writing the information is just the first step, harder still is to get it read, and most difficult is to find the information adopted. We need to research that key subject. The FDA ought to spend a few pennies of each user fee dollar they collect to study how to make the label as much a happening as the Leno monologue is to me, as broadly appealing as Finding Nemo, as great a conveyer of information as The Daily Show, as useful and motivating as Oprah, and as easy to understand as a New York Times headline.

Anesthesia has set the tone for patient safety and FDA processes before. Our organizations, with the guidance of Ellison C. “Jeep” Pierce, Jr. (Boston, Massachusetts; former president of the ASA and one of the founders of the ASA Patient Safety Foundation), built the foundation for the patient safety edifice; we and our drugs helped the Pilot Drug Unit at the FDA in the 1980s prove that a 180-day approval process was possible. We in anesthesia could—no, we should—construct another floor for this building: Someone needs to step forward to make labels understandable. Labels are too important to patient safety to wait for someone else to do it. The best outcome of the article by Chang et al. would be to motivate the FDA to use anesthesia pharmaceuticals to determine, with solid research and then regulation, how to write labels in a way that actually encourages reading and facilitates patient safety.

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Reference