

## CORRESPONDENCE

mer of hope by demonstrating a significantly shorter hospital stay in the thoracic epidural group *versus* the intravenous fentanyl group, it is difficult to place much emphasis on outcomes based on a small sample.

During the initial 48 h, Guinard *et al.* were able to demonstrate better preservation of pulmonary function in the patients treated with thoracic epidural fentanyl *versus* those treated with intravenous fentanyl. Unfortunately, their findings, although significant, were small in magnitude and did not appear to result in detectable improvements in radiologic or physiologic outcomes. It is difficult to interpret the value of postoperative pulmonary function studies in postoperative thoracotomy patients. The degree of surgical trauma to the remaining lung, the extent of the resection, a perioperative pattern of tobacco abuse or disuse, the presence and severity of reactive airways disease, and the quality of one-lung ventilation (separation) all affect the amount of lung function retained or lost in the early postoperative period. Much of this information was not available, and even if it were documented, it would be difficult to factor into an interpretable format. Thus, the relative preservation of pulmonary function, as indicated by the forced vital capacity, forced expiratory volume in 1s, and peak expiratory flow rate in the thoracic epidural fentanyl group, might be attributed to the presence of two lobectomy patients in the thoracic epidural group and the absence of any lobectomy patients in the intravenous fentanyl group. The greater number of pneumonectomy patients in the intravenous fen-

tanyl group may explain the greater loss of pulmonary function witnessed in this group. Pulmonary function studies in the early postoperative period may be useful in patients undergoing nonpulmonary surgery but must be regarded cautiously in intrathoracic surgery patients.

The findings reported by Guinard *et al.* are not the overwhelming endorsement for thoracic epidural fentanyl analgesia that I hoped for. Nevertheless, I will continue employ fentanyl for thoracic epidural analgesia. Perhaps patient-controlled epidural analgesia, with or without a local anesthetic, will provide the means to a more selective central neuraxis effect from epidural fentanyl.

**Frederick W. Burgess, Ph.D., M.D.**

Director, Anesthesia Pain Management Service  
Madigan Army Medical Center  
Tacoma, Washington 98431

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*In Reply:*—We appreciate the interest of Burgess for our study.<sup>1</sup> Based on our everyday practice, we also believe that our patients do better with thoracic epidural fentanyl analgesia after thoracotomy. More objectively, we have shown that their hospital stay may be reduced and that they need fewer rescue boluses. However, we can not escape from our results: when used alone, fentanyl consumption will not significantly be reduced by epidural infusion, even at the thoracic level.

We agree that pulmonary function may be influenced by numerous factors after thoracotomy, but we do not expect that a bias in randomization can explain the results of our study for the following reasons: (1) the type of surgery did not vary between groups, and (2) the best pulmonary function was observed in patients receiving thoracic epidural fentanyl despite the greatest number of pneumonectomies in this group (the incidence of pneumonectomies was not greater in patients receiving intravenous fentanyl as suggested by Burgess).

How can we reconcile our expectations and observations about epidural fentanyl use? Based on our data, a sample size of 833 patients will be required to detect a difference between intravenous and lumbar epidural fentanyl requirements (power of 0.8,  $P = 0.05$ , with a 33% difference between those two groups only). However, inclusion of such a large number of patients in this type of clinical study is impractical. Use of patient-controlled analgesia may reduce fentanyl consumption, but it is more expensive, is potentially more dangerous, and would not be expected to improve the quality of analgesia.<sup>2,3</sup>

The glimmer of hope concerning epidural fentanyl analgesia may rather come from: (1) concomitant epidural infusion of dilute local anesthetic solutions<sup>4</sup>; (2) addition of intravenous or oral nonsteroidal antiinflammatory drugs<sup>5</sup>; and/or (3) intraoperative use of epidural analgesia.<sup>6</sup>

**Jean-Phillipe Guinard, M.D.**

**Philippe Mavrocordatos, M.D.**

**René Chiolero, M.D.**

Service d'Anesthésiologie  
Centre Hospitalier Universitaire Vaudois  
1011 Lausanne, Switzerland

**Randall L. Carpenter, M.D.**

Department of Anesthesia  
The Virginia Mason Medical Center  
1100 Ninth Avenue, Mail Stop B2-AN  
P.O. Box 900  
Seattle, Washington 98111-0900

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## Are Histamine-releasing Drugs Really Contraindicated in Patients with a Known Allergy to Drugs?

*To the Editor:*—I have had the opportunity to read the correspondence between Doenicke and Laxenaire *et al.* presented in the March 1993 issue of ANESTHESIOLOGY.<sup>1,2</sup> The question raised by Doenicke, "Should atracurium be used in combination with propofol in patients with a history of allergy to drugs?" was not answered convincingly enough to reflect the title editorially assigned to the correspondence, "Atracurium Is Contraindicated in Patients with a Known Allergy to Drugs." For most clinicians the editorial banner may suggest the broader question: Is it appropriate to give a histamine-releasing drug to a patient with a history of drug allergy? As noted by Doenicke, many anesthetic drugs and adjuvants, including induction agents, opioids, muscle relaxants, many antibiotics, and even plasma expanders can cause the chemically mediated release of histamine.<sup>3\*\*†‡</sup> It is the rare anesthetic that does not require one or more of these drugs. Thus, there should be good clinical evidence before restricting the use of these drugs in patients with a history of allergy or asthma. The response by Laxenaire and her colleagues falls short of providing that evidence in several ways.

Although Laxenaire unquestionably has accumulated an extraordinary and useful epidemiologic anesthesia database and has been unable to uncover many important drug interactions, she does in fact study *life-threatening* reactions. Her own data suggest these occur once in every 3,500-5,000 anesthetics and that the majority of these severe reactions are immunologic and due to muscle relaxants.<sup>4</sup> Still these rare events occur only a few times in the clinical lifetime of most practicing anesthesiologists. A more practical question is

whether the histamine-releasing drugs we commonly use exhibit enhanced release in patients with a history of allergy, a population that may represent 30% of our patients. This common situation is very different from the relatively rare immunologic reaction described by Laxenaire *et al.* It may be that a clear and unequivocal answer to this question does not yet exist within our anesthetic literature.

Upon close reading, the mast cell and basophil studies referred to in Laxenaire *et al.*'s response fail to support her statement that "patients with allergic asthma release histamine more easily than a normal subject." The mast cells studies that are cited, and which purport to demonstrate that mast cells and basophils from patients with atopy have a greater tendency for histamine release, do not appear to be relevant to anesthetic drugs.<sup>5,6</sup> The manuscript by Findlay and Lichtenstein<sup>6</sup> describes basophil releasability in response to a number of pharmacologic agents (including mannitol and D<sub>2</sub>O). However, the authors relate that, whether derived from asthmatic patients or controls, the cells reacted identically to most stimuli. The article by Akagi and Townley<sup>5</sup> examines primarily spontaneous, not drug-induced, histamine release. The authors of these articles are appropriately and explicitly circumspect in applying their data in a more widespread fashion. Drugs that are used clinically in anesthesia were not evaluated in either experiment.

Because of the extraordinary tissue and species heterogeneity in mast cell content and releasability,<sup>7</sup> it would seem appropriate to perform these studies in human pulmonary mast cells from allergic and nonallergic patients exposed to various anesthetic agents. Such studies of human pulmonary mast cells have been published recently, although not specifically with the intent to uncover differences in mast cells of allergic and normal subjects.<sup>8,9</sup> Though these elegant studies are among the most useful mast cell studies in our literature, even here some findings seem inconsistent with clinical and plasma data. Certain drugs, such as vecuronium, which are devoid of clinically important histaminergic side effects and do not cause elevations of plasma levels, elicited histamine release in their preparations.<sup>8,10,11</sup> Thus, even these "ideal" mast cell preparations may not yield an answer to an important question.

\* Moss J: The impact of histamine research on clinical anesthesia and surgery. Agents Actions Special Conference Issue C135-C148, 1992.

† Laxenaire M, Moneret-Vautrin D: Allergy and anesthesia. *Curr Opin Anaesth* 5:436, 1992.

‡ Moss J: Adverse drug reactions caused by histamine, ASA Refresher Courses in Anesthesiology, Volume 20. Edited by Barash P. Philadelphia, JB Lippincott, 1992, p 263.