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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.[1,2] 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.[3,*,†,‡] 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.[4] 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.[5,6] The manuscript by Findlay and Lichtenstein[6] describes basophil releasability in response to a number of pharmacologic agents (including mannitol and D_2O). 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[5] 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,[7] 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.[8,9] 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.[8,10,11] 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.

Finally, the discussion of histamine-N-methyltransferase, the major enzyme of histamine catalysis, misrepresents published data. Although Laxenaire *et al.* are correct in stating that all relaxants can cause noncompetitive inhibition of histamine-N-methyltransferase and that its clinical significance has yet to be determined, the pharmacology of this inhibition has been well described by Harle *et al.* and by our group.[12,13] We first noticed this effect some years ago during the clinical trials of vecuronium but were unable to document it rigorously until the enzyme was sufficiently purified. We revisited the subject when several cardiac patients receiving slow infusions of vancomycin sustained precipitous hypotension after vecuronium was administered. Laxenaire *et al.* are correct in stating that all neuromuscular blocking agents, as well as a number of anesthetic drugs and adjuvants, can inhibit the enzyme, but the concentrations required for inhibition far exceed those that would be used clinically except for vecuronium, where the effect becomes manifest at 0.1–0.2 mg/kg.[12,14] Even then, our initial predictions were that this effect would be observed for 20–30 min after administration.

Laxenaire *et al.* have performed a tremendous service for anesthesia in their epidemiologic studies, but they have not responded to Doenicke's question to their conclusion about atracurium. As for the editorial banner, I would still like to see *direct and convincing* evidence demonstrating that anesthetic drugs that are relatively modest histamine releasers pose a greater risk in patients with a history of allergy or asthma before imposing a practice recommendation. In my own practice, I am persuaded that anesthetic depth and skill of the anesthesiologist may be more important than drug selection. At this point in the evolution of our literature, it would seem unjustified to place additional constraints on routine anesthetic practice without having sound outcome studies.

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Editorial Comment:—Dr. Moss's comments regarding the editorially assigned title to the letter from Doenicke[1] are absolutely correct. In neither the letter nor the article upon which the letter was based[2] was there a sufficiently compelling cause-effect relationship to justify the title, "Atracurium Is Contraindicated in Patients with a Known Allergy to Drugs." In fact, the title assigned by the Editor was similar to that suggested by Moss, "Is Atracurium Contraindicated in Patients with a Known Allergy to Drugs?" but was altered in the editorial process and unfortunately not detected before publication. An erratum is included in this issue of the Journal.

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Editor in Chief

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