Invited Commentary

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In their article, Ahlman and his colleagues have described well the clinical characteristics of gastric carcinoids. Their approach provides an excellent example of the integration of clinical and biochemical features necessary for the diagnosis and treatment of patients with complex endocrine syndromes such as those associated with foregut carcinoids.

While it has been long recognized that gastric carcinoids secrete histamine, this study adds conclusive documentation. The fact that both patients had elevated rates of urinary excretion of tele-methylimidazole (MeImAA, the major urinary metabolite of histamine) attests to the fact that their tumors produced and excreted this amine. On the other hand, the evidence that histamine is solely responsible for mediating all the symptoms is far less clear. The authors suggest that the duration of flush and the severity of the asthmatic attack induced by pentagastrin implicated histamine specifically and directly. In my experience, the duration and intensity of the response to pentagastrin provocation in the same patient varies enormously from study to study. Both serotonin and substance P, known to be secreted by carcinoid tumors, and kallikreins, for which the evidence of secretion is less secure, all induce bronchospasm. Hence, any of these carcinoid products, individually or in combination, may cause asthmatic attacks. In our earlier studies in patients with midgut carcinoids, calcium infusion invariably induced bronchospastic symptoms [1]. Thus, on clinical grounds alone, it is difficult to ascribe the symptoms described solely to histamine.

Provocative tests such as calcium infusion and pentagastrin administration have become integral components of the work-up of various forms of carcinoid disease. The theory underlying their use is that the provocative agents simultaneously stimulate the release of the pathogenetic modulator(s) and induce the characteristic symptom complex. Ideally, the correlation of augmented hormone levels and provoked clinical abnormalities would provide pathogenetic evidence linking the two. Unfortunately, this goal is rarely met. For example, in 2 recent studies on midgut carcinoid patients, there was no correlation between stimulated levels of serotonin and substance P and provoked symptoms [2, 3]. On the other hand, Roberts and colleagues documented a good correlation between changes in pulse and blood pressure and plasma histamine concentrations in a single patient with metastatic gastric carcinoid [4].

The authors warn that urinary excretion of MeImAA should always be measured before pentagastrin provocation is performed in patients suspected of harboring carcinoid tumors. While this sequence would certainly be ideal, I believe that there is a safe alternative. In hemodynamically unstable patients and those with severe and/or frequent episodes of flushing or asthma, we administer one-tenth of our standard pentagastrin dose (0.05 μg/kg) and inject the drug over 1–2 minutes rather than as a bolus. In our experience, this tiny dose of pentagastrin is adequate provocation and yet, it is quite safe and does not induce life-threatening complications.

Finally, a word about the therapy of carcinoid symptoms. As shown in this article by Ahlman et al., the use of blockers of H_1 and H_2 receptors abolishes or ameliorates symptoms associated with tumor-induced histamine release. Glucocorticoids are very effective in the treatment of patients with foregut carcinoids, particularly those originating from the bronchus; however, the reason for their efficacy is unknown. Although carcinoid patients have the high levels of prostaglandins [5], the action of steroids appears to be independent of their inhibition of prostaglandin biosynthesis.

Recently, 2 drugs have been developed that are effective in treating carcinoid symptoms. These were both utilized by Ahlman and colleagues. Ketanserin is a potent blocker of 5-HT_2 receptors which converts intestinal secretion to absorption [6]. Clinical studies have confirmed its usefulness in carcinoid patients [3, 7]. We have recently demonstrated that somatostatin abolished the diarrhea associated with the carcinoid syndrome [8]. This hypothalamic hormone or a long-acting analogue has been utilized successfully in patients with foregut carcinoids [4, 9, 10], providing a safe option in patients with severe gastrointestinal and hemodynamic symptoms.

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