

Correspondence

Intravenous heparin did not prevent exacerbations of hereditary angioedema in a patient on maintenance hemodialysis

To the Editor:

In a recent article concerning the safety and efficacy of inhaled and subcutaneous heparin versus that of placebo in the prevention of hereditary angioedema (HAE) attacks (in the June 2002 issue of *The Journal of Allergy and Clinical Immunology*), Weiler et al¹ demonstrated that commercial heparin (either subcutaneously injected or inhaled) was ineffective in preventing exacerbations of HAE. This conclusion was not in agreement with a previous uncontrolled study which suggested that heparin might be efficacious in preventing HAE attacks.² We have followed for a period of 6 months a patient affected with type II HAE (a positive family history, presence of signs and symptoms, low C4 antigenic level, and low C1-INH functional level) and chronic membranoproliferative glomerulonephritis (C3NeF-positive) who undergoes hemodialysis three times per week. At the time of the study, the patient could not receive danazol treatment for the prophylaxis of HAE attacks because of hepatitis C virus infection. Before the institution of each hemodialysis procedure, the patient's blood was anticoagulated with 5000 IU heparin administered intravenously; the patient therefore received 5000 IU heparin three times per week for the entire period of the study.

As well as in the other (100) patients followed in our Center for the Diagnosis and Treatment of HAE, swelling, difficulty in breathing, and abdominal pain were self-evaluated on a daily basis. Furthermore, either the patient or the investigators could evaluate symptoms throughout each dialysis procedure (4 hours) and during a follow-up period of 3 additional hours. Immunochemical and functional complement C1-INH and C4, complement C3, B and C4 cleavage fragments, classic and alternative pathways' functional activities, peripheral blood differential leukocyte count, and PO₂ were studied before, during, and after hemodialysis. It is known that leukopenia (neutropenia), hypoxemia, and complement activation can occur during hemodialysis and during hemoperfusion, notwithstanding the intravenous administration of heparin before the procedure.³

Despite chronic heparin administration, this patient experienced what were undoubtedly the highest intensity and frequency of HAE symptoms of any patient with HAE who was ever studied by us. Furthermore, leukopenia (neutropenia) and hypoxemia during hemodialysis were much more dramatic in this patient than in other patients undergoing similar hemodialysis procedures who were not affected with HAE. The severity of these manifestations can be ascribed to the concomitant presence in the patient of 3 conditions facilitating and/or causing complement activation (C1-INH deficiency,

C3NeF, and hemodialysis). The failure of intravenous heparin to prevent HAE symptoms in our patient further supports the conclusions of Weiler et al¹ that heparin (either subcutaneously injected or inhaled) is not effective in the prevention of HAE attacks.

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Reply

To the Editor:

Perricone et al¹ suggest that they have confirmed our observation that heparin lacks efficacy in preventing exacerbations of hereditary angioedema. Unfortunately, their patient had one other complement disorder—ie, the presence of nephritic factor—that complicated interpretation of the effects of heparin. In addition, they administered only 5,000 units of heparin 3 times per week rather than 10,000 units twice a day, as was the case in our study. Finally, though our study failed to demonstrate a statistically significant difference between subjects who received injected heparin and subjects who received placebo, there was a significant difference between subjects who received injected heparin and subjects who received inhaled heparin.

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Antifungal nasal washes for chronic rhinosinusitis: What's therapeutic—the wash or the antifungal?

To the Editor:

Ponikau et al¹ report an impressive improvement, both objectively and subjectively, in patients with chronic rhi-

nosinusitis (CRS). In the introduction to their article, they report that CRS is the most common chronic disease, having an impact on an estimated 37 million people per year in the United States (approximately 20% of the total population). In contrast, the patients who are the subject of their study universally had nasal polyps (90%) or polypoid changes by endoscopy (10% [5/51]); the reported prevalence of nasal polyps is much lower, ranging from 0.3% to 3.5%.¹ Eighty-eight percent of the patients in their study had undergone sinus surgery previously. The response of these patients to vigorous nasal washings might not be applicable to the larger pool of patients with symptoms of CRS who do not have surgically enlarged openings to the sinuses.

In the article's Fig 3, there appear to be only 12, not 13, patients with data regarding changes in mucosal thickening of the maxillary sinus. Could the authors clarify this figure?

As the authors point out, because of increased radiation risk and cost a posttreatment sinus computed tomography (CT) scan is usually not obtained. What were the indications for obtaining a sinus CT scan after the nasal washings in the 13 patients who did receive posttreatment sinus CT scans?

The authors rightly assert that a placebo-controlled trial is required before efficacy of their study irrigation can be attributed to the inclusion of an antifungal agent. Whereas 75% of patients showed improvement in clinical symptoms in the study by Ponikau et al,¹ similar degrees of improvement have been reported in studies using only hypertonic saline solution. In a study of 211 patients with a variety of causes for sinonasal symptoms, daily nasal pulsatile irrigation with hypertonic saline solution resulted in statistically significant improvement in 23 of 30 nasal disease-specific measures and quality of life in comparison with what was seen in a control group without nasal symptoms.² Heatley et al³ reported that daily nasal hypertonic saline irrigation through use of a bulb syringe or nasal irrigation pot and daily reflexology massage were equally efficacious and resulted in improvement in the symptoms of chronic sinusitis in more than 70% of subjects.³ Medication usage was decreased in approximately one third of participants, regardless of the intervention.

I am impressed with the inclusion in the study by Ponikau et al¹ of a great deal more detail and information on outcomes than was provided in other studies of nasal irrigation. However, I would like more information on how the authors assessed subjective improvement. Was a validated disease-specific or quality-of-life instrument used? Was it possible for the patients to indicate that any of their symptoms had worsened?

I congratulate the authors on their inclusion of many of the criteria required for critical assessment of a study.

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doi:10.1067/mai.2003.1481

Reply

To the Editor:

We thank Dr Ferguson¹ for raising important and insightful questions. We would like to respond to them as follows.

Regarding the prevalence of chronic rhinosinusitis (CRS): in its 1999 publication the National Institute for Health Statistics² noted that 37 million patients have chronic rhinosinusitis (CRS), which gives it a prevalence of 14.7%—not 20%, as estimated by Dr Ferguson.

A question was raised as to whether prior surgery was necessary to achieve the beneficial effects from amphotericin B irrigation. Indeed, as pointed out by Dr Ferguson, the majority of our patients did have nasal polyposis, now correctly termed *chronic hyperplastic rhinosinusitis*.³ The 51 patients in our report were refractory to other therapies; they were sequential, nonselected cases on 2 surgical services (E.B.K. and D.A.S.), but they were willing to participate in a clinical trial for intranasal antifungal agents instead of another course of surgical intervention. Because it is not unusual for a tertiary care institution, such as the Mayo Clinic, to see the more "severe" cases and because we consider nasal polyposis the end stage of the chronic inflammatory process driving CRS, it is not surprising that our patient population probably includes more patients with polyposis than are seen in a general otorhinolaryngologist's office. However, we also point out that 4 (67%) of 6 patients, who are among our 51 patients and did not have prior surgery, also improved with amphotericin B irrigation. Therefore, a surgically enlarged opening to the sinuses is probably not necessary for beneficial effects of the treatment.

Dr Ferguson's critique that our Fig 3 demonstrates only 12 patients, not the 13 that we claim, is probably explained by the fact that the publisher needed to reduce the size of the figure. Therefore, overlapping data points and lines are not well visualized. However, an enlarged version of the same figure clearly shows the data for all 13 patients that we presented. We have provided a high-resolution copy of our Fig 3 to allow Dr Ferguson to examine all 13 data points.

Another question was raised regarding the indications for the second computed tomography (CT) scans. In addition to being followed by 2 surgeons at the Mayo Clinic