Efficacy and Safety of Inhaled Insulin Therapy

TO THE EDITOR: The study by Rosenstock and colleagues (1) included patients with type 2 diabetes who had a wide range of body mass index (BMI) measurements. In patients with type 2 diabetes, obesity is associated with poor treatment response to insulin (2). Because higher BMI may be a potential confounder of the study’s primary outcome (change in hemoglobin A1c level from baseline), we recommend an analysis that is based on predefined BMI strata to distinguish the effects of inhaled insulin among patients of various body types. In addition, analysis of the confounding effects of dietary restriction and exercise regimens on diabetes control is necessary.

As in any open-label study, performance and observation biases of the investigators and the unblinded patients who received the new inhaled insulin treatment may substantially affect outcome measurements (3). Furthermore, mean outcome hemoglobin A1c levels are affected by outlying measurements that can increase error rates and cause alteration of estimates in statistical testing (4). Therefore, readers would benefit from knowing the distribution of the hemoglobin A1c levels of the study groups before and after treatment.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: Like many general internists, we have had our interest piqued about inhaled insulin therapy for several years. Because data have eked out slowly, generally through endocrinologic publications and meetings, we were delighted to see the issue addressed recently in “our journal” (1). However, after reading the article, we were disappointed by the design of the study and wonder about the editors’ decision to publish it at this particular time.

We have 3 concerns about the authors’ methods. First, the study was unblinded, which could have introduced conscious and unconscious biases. This shortcoming could have been avoided if the investigators had provided a placebo inhaler to patients in the group that continued to take oral agents. Second, the control group was clearly not responding to their regimen. A more rigorous approach would have been to compare the clinical standard of care (that is, the addition of a dose of intermediate-acting insulin at bedtime). Third, the study was too short to assure our concern about pulmonary outcomes or metabolic worsening that may result from long-term insulin therapy.

As designed, the study shows that patients who no longer respond to oral antidiabetic agents may achieve impressive short-term glycemic control with the addition or substitution of inhaled insulin therapy. Most physicians have been aware of the efficacy of insulin in this setting but only prescribe insulin as a last resort because of the potential for hyperinsulinemia and weight gain.

We could not help but notice that the study was conducted 7 years ago (troglitazone could be part of the dual regimen) and that the publication date of 18 October 2005 coincided with the U.S. Food and Drug Administration (FDA) deliberations regarding approval for inhaled insulin. Could the anticipated media interest surrounding the FDA decision have influenced the editors’ enthusiasm for publishing the article at this time?

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Potential Financial Conflicts of Interest: None disclosed.

Reference

IN RESPONSE: As a matter of editorial policy, we avoid doing anything that people would interpret as collusion with a commercial company to draw attention to their product. In the case of Rosenstock and colleagues’ paper (1), we knew that the FDA had not yet approved inhaled insulin, but we had no idea when it would announce its decision. We could not and did not engineer the publication date to coincide with the FDA announcement.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

IN RESPONSE: We agree that a limitation of our study was the open-label design. However, a double-blind study was not feasible because 1) it was not possible to manufacture a suitable placebo for inhaled human insulin, 2) it seemed inappropriate to blind treatment when individualized flexible-dose titration is needed, and 3) patients or physicians would have very easily unblinded the placebo or inhaled insulin because of the latter’s immediate effect on blood glucose levels.
Ours was a proof-of-concept study that was designed in 1998 according to good clinical practices at the time and was based on a previous study of similar design (1). We do not believe there were any ethical issues for patients who were randomly assigned to the control group because microvascular complications are associated with long-term hyperglycemia, and there is no evidence that a relatively short period of inadequate glucose control will have a deleterious effect. The reality is that many patients who have type 2 diabetes with poor glycemic control continue to take oral agents instead of initiating insulin therapy (2). We continued the study for 3 months to provide sufficient time to show an effect (1) while minimizing the control group’s exposure to hyperglycemia. Furthermore, all participants had the option of receiving inhaled human insulin by enrolling in an open-label extension of the trial.

In response to concerns regarding the timing of the publication, we would like to reaffirm the editor’s reply and definitively state that the publication of this paper was not engineered to coincide with the FDA Advisory Committee’s report. Indeed, the paper was subjected to 2 rounds of review by the Annals editors over several months, which also required the submission of additional analyses; therefore, it would have been impossible to predict if publication would coincide with the FDA Advisory Committee’s report.

As highlighted in Dr. Comi’s editorial in the same issue (3), we were also pleasantly surprised at the robust response to inhaled human insulin despite what might seem to be a nontraditional approach. Furthermore, the effects observed with inhaled human insulin extended beyond the predicted pharmacokinetic activity by substantially improving fasting plasma glucose levels, which probably contributes to the robust reductions of hemoglobin A1c levels.

Inhaled human insulin could really have an impact if health care professionals can convince adult patients with type 2 diabetes to begin using insulin much earlier and more aggressively. The availability of the product as a treatment option has already been shown to substantially increase the proportion of patients who would theoretically choose to begin insulin therapy if they cannot achieve glycemic control with a modified diet or oral antidiabetic agents (4). We agree with Dr. Comi’s viewpoint that patient acceptance and preference will ultimately determine the future use of inhaled insulin.

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References

Survivor Costs in Cost-Effectiveness Analysis

TO THE EDITOR: Golan and colleagues (1) present a cost-effectiveness analysis of several anti-Candida strategies for high-risk patients in the intensive care unit. They evaluate treatment effectiveness by the number of life-years that are gained from reduced hospital mortality rates. The authors included initial hospitalization costs in their calculations. This approach, however, overestimates treatment cost-

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effectiveness and provides unduly favorable cost-effectiveness ratios. When treatment effectiveness is assessed by the number of life-years gained, costs for health care services that are required to provide this gain must also be included (2). After all, the anti-
*Candida* therapy and the initial hospital stay are responsible not only for the life-years gained but also for health care services that are delivered in the years between hospital discharge and death. Therefore, the appropriate approach is to include all health care costs (or at least those responsible for life extension) that are incurred during the period between hospital discharge and death.

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**Potential Financial Conflicts of Interest:** None disclosed.

**References**
1. Golan Y, Wolf MP, Pauker SG, Wong JB, Hadley S. Empirical anti-

**IN RESPONSE:** Dr. Gandjour raises an interesting point: The exclusion of survivor costs (costs associated with a treatment because it extends the patient’s life) could affect the calculated cost-effectiveness ratio. He suggests that we calculated unduly favorable cost-effectiveness ratios because we excluded such costs.

The purpose of cost-effectiveness analysis is to provide a metric of comparison of potential uses of limited resources (the “medical commons” [1]). There is no gold standard for the threshold of willingness to pay. To be useful, such analyses must use standard methods, as we have done (2).

In response to Dr. Gandjour’s suggestion, we searched PubMed to identify all cost-effectiveness analyses that were published in 5 major medical journals (JAMA, *Annals of Internal Medicine*, *The New England Journal of Medicine, Lancet*, and *British Medical Journal*) from 1 January 2003 to 31 December 2005. Of 43 articles that we identified, only 2 included survivor costs; in both articles, these costs were partial and disease-unadjusted.

Nyman (3) found little consensus regarding the inclusion of survivor costs in cost-effectiveness analysis. Even those researchers who favor the inclusion of such costs disagree on the type of costs to be included. Consequently, a dependable method that enables the inclusion of survivor costs has not been developed. Furthermore, the inclusion of such costs would bias analyses toward nonintervention unless an adjustment of willingness-to-pay thresholds occurred.

When the calculated cost-effectiveness ratio is close to the acceptable threshold and the survivor’s future cost of care is expected to offset future earnings, the addition of survivor costs could transform an otherwise cost-acceptable intervention into an unacceptably expensive one. Invasive candidiasis in patients in intensive care units, the focus of our analysis, has been associated with a high mortality rate and shortened life expectancy. Both of these factors were incorporated into the analysis, but impaired future productivity was not. If one includes survivor costs, then such productivity might also be included. Therefore, the inclusion of survivor costs would make our analysis less useful and generalizable without affecting our conclusion that selective empirical use of anti-
*Candida* therapy in patients in the intensive care unit is a reasonable strategy.

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**CLINICAL OBSERVATIONS**

**Evidence for Vascular Spread of Varicella Zoster–Associated Vasculopathy**

**TO THE EDITOR:** Background: Varicella zoster virus (VZV) infection may provoke life-threatening cerebrovasculopathy. Diagnosis in immunocompromised patients is often complicated because of the possibility of multiple infections (1, 2). We present unique magnetic resonance angiographic images of VZV-associated cerebrovasculopathy in an immunocompromised patient.

**Case Report:** A 36-year-old homosexual man with HIV infection was hospitalized for evaluation of convulsions. He had a vesicular rash on the right knee, redness and itching sensations in the right eye (herpes zoster ophthalmicus), neck stiffness, and a temperature as high as 38°C. Neurologic examination revealed memory loss and inability to perform simple arithmetic. The patient did not have ptosis, significant vision loss, or ocular cranial nerve palsies. Results of laboratory studies revealed a CD4 cell count of 0.036/μL, and a temperature as high as 38°C. Neurologic examination revealed memory loss and inability to perform simple arithmetic. The patient did not have ptosis, significant vision loss, or ocular cranial nerve palsies. Results of laboratory studies revealed a CD4 cell count of 0.036/μL.

Magnetic resonance angiography showed multiple cerebral arteries (Figure, panel A). T2-weighted images showed a stenotic lesion in the left middle cerebral artery with areas of high intensity in the left corona radiata, which suggested an infarction in the region of...
the left middle cerebral artery. Subsequent magnetic resonance imaging (contrast-enhanced T₁-weighted images) showed multiple enhanced lesions of cerebral arteries (Figure, panel B); fluid-attenuated inversion recovery sequences showed higher-intensity perivascular areas within subcortical regions that suggested angioedema (Figure, panel C). A diagnosis of VZV-associated cerebrovasculopathy was made, and prednisolone (80 mg/d) was administered. The paralysis and other neurologic symptoms resolved. Magnetic resonance imaging showed decreased T₂-weighted signal intensity in the left frontal lobe. On day 28, results of laboratory studies were normal, and VZV antibodies were not detected in the cerebrospinal fluid. All treatments were withdrawn, and the patient was discharged.

Discussion: Increased serum and cerebrospinal fluid levels of VZV-IgG; the detection of VZV-DNA in cerebrospinal fluid by polymerase chain reaction testing; magnetic resonance evidence of cerebrovascular involvement; and improvement in neurologic manifestations in response to the elimination of VZV from the cerebrospinal fluid strongly suggest that cerebrovasculopathy in this patient was caused by VZV infection. However, the patient presented with involvement of his eye and ipsilateral paralysis, even though herpes

Figure. Magnetic resonance angiography and imaging in an immunocompromised patient with varicella zoster virus-associated cerebrovasculopathy.

A. Magnetic resonance angiography demonstrates multiple aneurysms along cerebral arteries (arrows) primarily localized in the peripheral smaller arteries and a stenotic lesion in the middle cerebral artery. B. Contrast-enhanced T₁-weighted image shows multiple enhanced lesions of cerebral arteries (arrows). C. Fluid-attenuated inversion recovery sequence shows multiple areas of higher-intensity perivascular areas in subcortical regions, which suggests angioedema.
vzor ophthalmic (or VZV infection transmitted through the trigeminal nerve) often results in a contralateral neurologic symptom (1–3). In addition, in patients with herpes zoster ophthalmic, magnetic resonance angiography typically shows a unifocal lesion that tends to be localized within or near the circle of Willis, probably because of the anatomical proximity of the trigeminal nerve to the circle of Willis. However, magnetic resonance imaging showed that our patient had not only a stenotic lesion in the left middle cerebral artery but also multiple aneurysmal lesions along the cerebral arteries. Furthermore, these aneurysmal lesions were distributed from the proximal to the distal cerebral arteries. These features suggested that the VZV virion had spread through cerebral arteries and not through the trigeminal nerve.

**Conclusion:** This case of VZV-associated vasculopathy that caused multiple aneurysmal lesions in smaller peripheral arteries and a stenotic lesion in the left middle cerebral artery of an immunocompromised patient suggests that the virion spread through the circulatory system and not through the trigeminal nerve.

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**References**


**Reconstitution of Hemin for Intravenous Infusion**

**TO THE EDITOR:** Background: Hemin, the preferred treatment for acute porphyrias (1), is available in the United States as lyophilized hematin (Panhematin, Ovation Pharmaceuticals, Deerfield, Illinois) and is reconstituted with sterile water just before infusion. The product package insert recommends that treatment be administered through a large arm vein or by central venous catheter to avoid phlebitis.

Many physicians and medical centers have adopted the published method of Bonkovsky and colleagues (2) for reconstituting hematin with 25% human albumin. Each albumin molecule has a single high-affinity heme binding site and additional lower affinity sites. This reconstitution method uses an equimolar amount of albumin to optimize the stability of hemin as heme albumin and to prevent formation of degradation products that lead to unwanted side effects, including phlebitis at the site of intravenous infusion and transient coagulopathy. Many health care providers have requested detailed instructions for this method of reconstituting lyophilized hematin with albumin.

**Objective:** To facilitate optimal treatment by providing a detailed description of the method that the authors have used for reconstituting hematin with albumin and for administering the product as heme albumin.

**Methods:** A stable hemin solution is prepared by reconstituting lyophilized hematin with 132 mL of 25% human serum albumin instead of sterile water. It is important not to add sterile water before the albumin because this will immediately lead to degradation products. The following materials are needed for the procedure: 313-mg vial of lyophilized hematin, 150-mL sterile empty glass bottle for infusion, three 50-mL vials of 25% albumin (only 132 mL will be used), 5-micron filter needle, and a vent needle.

To prepare the hemin for infusion:

1. Reconstitute the 313-mg vial of lyophilized hematin with 132 mL of 25% albumin. Because this volume will almost completely fill the vial, the albumin must be injected into the vial slowly and the vial must be vented. Use a vented needle or make a vent with a separate needle to release the air pressure.

2. Do not shake the mixture. Swirl the vial 15 to 20 times to ensure that it is thoroughly mixed (it will be difficult to see if the materials are blended because of the dark color of hemin).

3. After reconstitution, the hemin concentration is 2.4 mg/mL. The volume required to deliver the desired dose (usually 3 to 4 mg/kg of body weight) should be calculated according to representative volumes for corresponding body weights (Table).

4. Withdraw the required dose into a syringe by using a 5-micron filter needle.

5. Inject the dose into a 150-mL empty sterile bottle.

6. Label the bottle.

7. Place the bottle in an amber bag to protect the mixture from light. Also place a vented spike adapter in the bag. Affix a yellow Medication Administrations Recording blood products label (for both albumin and lyophilized hematin) to the amber bag, and then place the amber bag inside a STAT-labeled bag.

8. Hand-deliver the bag to the clinical unit immediately. Once mixed, the drug is considered stable for 1 hour. The heme–albumin complexes may be stable for much longer, but these solutions do not contain bacteriostatic agents and should be infused within about 1 hour of preparation.

To infuse the heme–albumin mixture, a large peripheral vein should be used. A peripherally inserted central catheter, central line,

**Table. Representative Volumes of Heme–Albumin Solution Needed To Achieve Desired Hemin Dosage**

<table>
<thead>
<tr>
<th>Patient Body Weight, kg</th>
<th>Desired Hemin Dosage of 3 mg/kg Daily</th>
<th>Desired Hemin Dosage of 4 mg/kg Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemin, mg</td>
<td>Heme–Albumin Mixture, mL</td>
</tr>
<tr>
<td>50</td>
<td>150</td>
<td>63</td>
</tr>
<tr>
<td>60</td>
<td>180</td>
<td>75</td>
</tr>
<tr>
<td>70</td>
<td>210</td>
<td>88</td>
</tr>
<tr>
<td>80</td>
<td>240</td>
<td>100</td>
</tr>
</tbody>
</table>

* For a single dose, use of more than 1 vial of lyophilized hematin (313 mg) is seldom recommended.
or central port may be used if available. The heme–albumin dose is generally infused by piggyback to an intravenous line that is infusing 0.9% sodium chloride at a moderate rate. The dose should be infused over a period of at least 60 minutes or at a rate that should not exceed 1 mL/min, which corresponds to the recommendation for infusing 25% human albumin (3, 4). A somewhat shorter infusion time may be acceptable but may entail some risks from intravascular volume expansion. Some patients have experienced headaches shortly after infusions of heme–albumin, perhaps related to transient expansion of intravascular volume. Specific recommendations on the use of inline filters with heme–albumin are lacking; if any filter is to be used, we recommend a coarse filter for particulate matter instead of a fine filter for bacteria to avoid slowing the infusion. After the heme–albumin is infused, the infusion of 0.9% saline should be continued for about 10 minutes to clear the line and vein of the drug. If a central line or port was used, this should also be cleared of heme–albumin after the infusion.

Discussion: Reconstitution of lyophilized hematin with albumin is recommended, particularly when a dose is to be infused into a peripheral vein. This prevents formation of degradation products that bind to endothelial cells, platelets, and coagulation factors. In our experience, this method reduces the frequency of phlebitis at infusion sites and helps to prevent progressive loss of venous access in patients with frequent attacks who require repeated hemin infusions. Reconstitution with albumin also prevents transient coagulopathy, which is sometimes associated with bleeding (5). Although coadministration of hematin and albumin is not approved by the U.S. Food and Drug Administration, it offers the advantage of preventing these side effects. Heme arginate, which is available in Europe and South Africa, is more stable after dilution and is less likely to cause phlebitis and coagulopathy (5); however, reconstitution with albumin instead of saline has also been recommended for this product to preserve peripheral veins (6).

The currently recommended regimen for treating acute attacks of porphyria is hemin, 3 to 4 mg/kg, daily for 4 days. Extended treatment is indicated in some cases, particularly if there is advanced neuropathy (1). Although the package insert for Panhematin recommends a wider dose range of 1 to 4 mg/kg, most experts in the field believe that daily doses less than 3 mg/kg are probably less effective. Twice-daily administration probably has no advantage over a once-daily regimen. A single dose should not exceed 4 mg/kg or 313 mg (the contents of 1 vial). Hemin is initially distributed in plasma and is then taken up primarily in the liver. Because little is distributed in fat or other tissues, a single dose for an obese patient should seldom if ever exceed a single 313-mg vial. No more than 6 mg/kg should be given in a 24-hour period.

A regimen of hemin therapy for prevention of attacks has not been established. Administration of 3 to 4 mg/kg once or twice weekly (7) (or during the premenstrual period for women with frequent episodes that occur in a cyclic pattern) has been effective in some patients.

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References

Correction: Combination Pharmacotherapy for Cardiovascular Disease

Correction: A meta-analysis on protein and energy supplementation in older adults (1) contained an error. The second sentence in the second paragraph of the Results section should have read, “The interventions in the trials aimed to provide between 175 kcal (732 kJ) and 1000 kcal (4.2 MJ) and between 10 g and 37 g of protein daily.” In Appendix Table 2 (available at www.annals.org), the data in the second column (Energy and Protein Content) for the Feed Or Ordinary Diet (FOOD) trial should have read, “540 kcal and 22.5 g of protein daily.”

Reference