Inhaled Insulin: A Proof-of-Concept Study

TO THE EDITOR: The editorial (1) about our article on insulin therapy (2) requires some clarification because information that answers many of the issues raised was not available to the editorialist. Ours was a proof-of-concept study. Half of the participants in this open-label, controlled study were randomly assigned to remain on their preexisting treatment. The study tested the hypothesis that a regimen containing inhaled human regular insulin as the rapid-acting formulation provided glucose control as good as that of a conventional insulin regimen in patients with type 2 diabetes currently receiving such a regimen. Given the preliminary, albeit interesting, nature of the study, the Annals editors suggested that the research could best be presented as a brief communication showing the efficacy of a regimen including inhaled insulin compared with each patient’s own baseline values. The editorial comments on lack of a control group are based on only part of the data.

Our study did indeed have a control group (2). Specifically, 27 patients were randomly assigned to receive continued subcutaneous insulin. After 12 weeks, the mean (±SD) unadjusted change in hemoglobin A1c values among these 27 patients was −0.7 ± 0.7 percentage point. This change was not statistically significantly different from the change in the inhaled insulin group (−0.7 ± 0.7 percentage point). Hypoglycemic events were also similar between the groups. The patients receiving inhaled insulin had a crude event rate of 0.8 event per patient-month, whereas the subcutaneous group had 1.1 events per month. The difference between the groups was not significant. Although the inhaled insulin group lost weight (change, −0.2 ± 3.3 kg) and the subcutaneous group gained weight (change, 1.3 ± 2.1 kg), this difference also did not reach statistical significance. As a safety measure, pulmonary function studies were done before and after 3 months of treatment, and these results did not change. We did not include this information in the published brief communication because of space limitations. Follow-up of these patients has continued for well over 2 years, and the data, presented at the European Association for the Study of Diabetes, indicate good toleration (3).

The editorial also raises a concern that the decrease in hemoglobin A1c levels was “disappointingly modest.” The study was designed for equivalence; therefore, it evaluated patients already receiving an insulin regimen that provided baseline hemoglobin A1c levels of 0.07 to 0.119 (7.0% to 11.9%), and its design was based on maintaining glucose control to similar targets (5.55 to 8.88 mmol/L [100 to 160 mg/dL]) in both groups (targets that would not be expected to alter hemoglobin A1c in either group).

Finally, the editorialist comments on the fact that bioavailability of inhaled insulin was 10% of the bioavailability of subcutaneous insulin. This is clearly not ideal; however, all alternative delivery systems have this problem. This system loses insulin at every step along the delivery system pathway (for example, from the device to the oropharynx and then swallowed). Thus, the bioavailability of the expired material is substantially greater than the overall figure quoted.

A major philosophical issue raised by the editorial is whether insulin treatment of type 2 diabetes is misdirected. This issue is debatable, and such a discussion exceeds the scope of this brief response. However, a substantial proportion of adults with type 2 diabetes remain significantly hyperglycemic, and the disease continues to progress despite all efforts, including combination oral therapy. Good glucose control is the ideal in such patients, and the evidence supports the role for glycemic control in reducing complications and the long-term safety of insulin in this role.

This phase II study indicates that this technology appears to maintain glycemic control similar to that provided by subcutaneous insulin and that pulmonary function remains stable. Phase III studies of inhaled insulin are ongoing, and we look forward to presenting these data to Annals readers in the future.

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sured bone mineral density (BMD) of the hip. Their investigation of the relationship between body size and fracture risk in the Study of Osteoporotic Fractures revealed that if hip BMD has been measured, body size measurement provides no additional predictive power. These conclusions are valid only for DXA-determined BMD.

Standard DXA provides an areal BMD (aBMD), a ratio of bone mineral content to the projected area of the region of interest. Bones of equal volumetric BMD but unequal sizes have unequal aBMDs: Large bones have higher aBMDs (2). As measured by standard DXA, BMD is a compound measure reflecting both bone size and mineral content. The compound nature of aBMD contributes to DXA’s ability to predict fracture risk because bone size is a component of bone strength (3). Bone mineral density assessed by quantitative computed tomography or estimated by ultrasonography does not depend on bone size.

Clinicians should remain aware that not all BMDs are alike and that one important difference among them may be their correlation (or lack thereof) with body size. Physicians using size-independent densitometric methods should continue to use body size as a distinct fracture risk factor.

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IN RESPONSE: Dr. Blank notes that DXA is not a volumetric measurement of BMD. He cites evidence that BMD of the lumbar vertebrae as measured by DXA is correlated with height and weight, whereas volumetric BMD measurements are not (1). He suggests that this may explain our finding that the associations between larger body size and risks for hip, pelvis, and rib fractures are eliminated by adjustment for hip BMD since DXA measurement captures bone size as well as BMD.

To test this hypothesis, we did additional proportional hazards analyses of the associations between total body weight and risks for hip, pelvis, and rib fractures. By using the same approach as reported in Table 2 of our paper, we tested one set of models by adding height at visit 2 to the existing adjustments for age, smoking status, physical activity, history of falls, estrogen use, and health status. We then tested a second set of models that included an additional adjustment for total-hip BMD. The adjustment for height as a proxy for bone size did not affect our results or conclusions. After adjustment for height, age, smoking status, physical activity, history of falls, estrogen use, and health status, women in the lowest quartile of weight (<57.8 kg) compared with those in the upper quartile (>73.3 kg) had an increased risk for hip fracture (odds ratio [OR], 2.1 [95% CI, 1.5 to 3.0]), pelvis fracture (OR, 2.7 [CI, 1.3 to 5.6]), and rib fracture (OR, 2.0 [CI, 1.2 to 3.2]). After further adjustment for BMD, the point estimates of risk were reduced and no longer reached statistical significance (OR for hip fracture, 0.9 [CI, 0.6 to 1.3]; OR for pelvis fracture, 1.5 [CI, 0.7 to 3.3]; OR for rib fracture, 1.3 [CI, 0.7 to 2.2]).

Irrespective of the mechanism for the relationship between body size and risk for fracture, the clinical implications of our findings are unchanged. Dual-energy x-ray absorptiometry is the current standard for BMD measurement in clinical practice. The effect of adjustment for volumetric density on the association between body size and risk for various fractures remains to be investigated.

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Airway Adrenaline in Patients with Severe Cardiac Disease

TO THE EDITOR: Raymondos and colleagues (1) report a substantial increase in blood pressure after airway administration of adrenaline in 34 patients undergoing general anesthesia. We noted a discrepancy between the data reported in the Results section of the text and those presented in the authors’ Figure (1): The Figure clearly demonstrates that an undecipherable number of patients had an initial decrease in blood pressure, a response that is not mentioned anywhere in the text. We have previously shown that an initial decrease in blood pressure, such as that displayed in the authors’ Figure, is caused by β2 stimulation and may be deleterious during cardiac arrest (2). Other laboratory and clinical reports on endotracheal adrenaline administration disregarded the same initial β2-mediated effects, causing hypotension induced by...
Peripheral vasodilatation unopposed by $\alpha_2$-receptor–mediated vasoconstriction. Higher endotracheal doses as first-line therapy in cardiac arrest should be further investigated.

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IN RESPONSE: Paret and colleagues speculate that the effects of endotracheal adrenaline may cause $\beta_2$-mediated hypotension that could be deleterious during cardiac arrest. In our study, the frequency of initial decrease in blood pressure did not differ after airway administration of adrenaline compared with intravenous administration. Blood pressure decreased by 10% in 4 of 34 patients 30 seconds after airway-administered adrenaline but also decreased by 10% in 6 of 34 patients after intravenously administered adrenaline ($P > 0.2$). This indicates that the blood pressure decrease is not related to the route of adrenaline administration but may be associated with the plasma adrenaline levels achieved. In fact, initial plasma adrenaline levels were not different 30 seconds after airway adrenaline or 30 seconds after intravenous adrenaline ($P = 0.1$; Figure).

The blood pressure decrease at low plasma levels was immediately opposed by $\alpha$-receptor–mediated vasoconstriction at rapidly increasing plasma adrenaline levels (Figure). The blood pressure decreases observed by McCrirrick and Kestin were probably caused by the anesthesia technique because the endotracheal adrenaline dose of 30 $\mu g$ was too low to produce any effects (1). In dogs, blood pressure decreases persisted for 30 minutes after endotracheal administration of adrenaline (2). We speculate that this effect was associated with low plasma adrenaline levels because of poor effectiveness of the adrenaline administration technique. In our study, plasma adrenaline levels also remained low after airway administration of adrenaline in 4 of 13 patients (Figure). However, as stated in our report, spontaneous plasma adrenaline levels in cardiac arrest are even higher than the maximum plasma levels achieved in our study (Figure). It is extremely unlikely that adrenaline administration during cardiac arrest could cause the $\beta_2$-mediated vasodilatory effects that might occur in patients with spontaneous circulation at low plasma adrenaline levels. Therefore, vasodilatory effects after airway adrenaline do not appear to be clinically relevant.

In contrast, the unreliable adrenaline absorption from the lungs does represent a relevant clinical problem. The course of plasma adrenaline levels varied considerably after airway administration of adrenaline (Figure), and a greater variation could be expected during cardiac arrest. We doubt that higher endotracheal adrenaline doses would result in more reliable adrenaline absorption from the lungs.

Figure. Time course of plasma adrenaline levels.

Levels were measured in six patients (top) after central intravenous adrenaline administration (CV) and application directly into the endotracheal tube (ET) and in seven patients (bottom) after central intravenous and peripheral bronchial (PB) administration by way of a wedged catheter. The bold line represents the median.

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Therefore, our data may encourage researchers to consider more reliable routes for adrenaline administration in adults (for example, the intraosseous route) and to investigate alternative vasopressors that are absorbed more reliably.

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References

TO THE EDITOR: Salary Equity among Male and Female Internists

TO THE EDITOR: In their survey of general internists and specialists in Pennsylvania, Ness and colleagues (1) purport to demonstrate a 14% earnings discrepancy between male and female physicians after adjusting for confounding variables. Women are also described as being disproportionately represented in low-earning specialties.

This study has several problems. First, the authors, by their own account, did not query respondents on the number of weeks worked per year. In a previous study (2), male physicians reported working 47 weeks per year and female physicians, 46. Assuming similar habits in Ness and colleagues’ study, the salary differential decreases to 11.5%.

Second, the authors did not describe how an hour is spent. Differences in “productivity,” such as numbers of patients seen per hour and numbers of procedures done, may explain some or all of the remaining earnings differential.

Third, no information is provided on features of practice that might affect income: for example, participation in night and weekend call and provision of hospital care versus reliance on hospitalists. Many group practices allow physicians to opt out of call coverage, with an associated offsetting expense.

Finally, the suggestion that women may congregate in low-paying specialties through forces other than their own choosing is unsubstantiated. Our community includes female general internists, allergists, and endocrinologists but also gastroenterologists, cardiologists, general surgeons, and otolaryngologists. A more plausible explanation is that female physicians make voluntary tradeoffs between compensation and lifestyle.

Unfortunately, Ness and colleagues do not adequately probe their respondents to determine why income differs between male and female internists. Without this information, the reader must ponder whether reasonable factors, such as number of weeks worked per year, individual productivity, and voluntary lifestyle tradeoffs account for this differential. Undocumented allegations of sex discrimination are more difficult to accept. After all, payments are no different for services rendered by Dr. Jane Doe or Dr. John Doe.

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IN RESPONSE: We appreciate Dr. Ross’s comments. As with most research, our analysis leaves as many important questions unanswered as answered. In this case, the relevant questions relate to the economic, social, and cultural factors driving salary inequity.

Dr. Ross cites three factors that may have confounded our results: weeks worked per year, productivity, and voluntary lifestyle tradeoffs. Dr. Ross himself shows that number of weeks worked per year would not eliminate the observed effect. His further point about productivity was considered in a 1999 survey published by Physician’s Weekly, based on a poll of physicians from the Medical Group Management Association, the United States’ largest organization of physicians working in group practices (1). Although women did report seeing fewer patients per year, in part because of fewer working hours and in part because they spend more time with each patient, patient load could not account for the salary gap observed. For example, among noninvasive cardiologists, after adjustment for patients seen, men earned $163 per case and women earned $144 per case. The final issue Dr. Ross cites as a possible confounder is voluntary lifestyle tradeoffs leading to choice of subspecialty and practice type. To avoid confusion, we reiterate that even after adjustment for differences in professional niche, women were less well compensated than men. Had we not adjusted for this, the salary differential would have been far greater than the adjusted 14% we reported.

Do cultural and social factors influence decision making, and are men and women similarly influenced? Ample data suggest that women, particularly those with children, face major obstacles in career trajectory that men do not face (2, 3). For instance, even among dual-physician couples, women are more likely to report changing their schedules to accommodate child care responsibilities (4). In these couples, women more often reported limiting professional life for family reasons and men more often reported that their career had taken precedence over their spouse’s. This would be fine if women made these decisions freely and contentedly. But women have been shown to experience more frustration over competing work and home life demands than men (3). Thus, the assertion that women deserve lower pay because of voluntary decisions is truly an undocumented allegation. It depends on the meaning of “voluntary.” Cul-

References
Isoniazid-Induced β-Hydroxybutyric Acidosis

TO THE EDITOR: We read with interest Miller and colleagues’ report on lactic acidosis associated with stavudine (1). We report our recent experience with nucleoside-induced lactic acidosis complicated by isoniazid-induced β-hydroxybutyric (BHB) acidosis.

In late 1999, HIV infection was diagnosed in a 29-year-old obese African-American woman after she presented with Pneumocystis carinii pneumonia. Her CD4 cell count at diagnosis was 0.025 × 10^9 cells/L, and her viral load was 100 000 RNA copies/mL. In early January 2000, she began receiving stavudine, lamivudine, and efavirenz. This regimen promptly suppressed viremia, with a concomitant increase in CD4 cell count. After reconstitution of her immune system, the patient gained 28 kg. After 4 months of highly active antiretroviral therapy, she began receiving isoniazid prophylaxis, 300 mg daily, plus vitamin B6 (pyridoxine, 50 mg daily) because of a previous positive purified protein derivative test for which she had not received treatment. Liver function test results were normal 3 months after isoniazid prophylaxis began.

Three weeks before the hospitalization reported here, the patient developed nausea, vomiting, and vague abdominal pain. She presented to the emergency department because of progressive symptoms. Work-up revealed a serum bicarbonate level of 10 mmol/L, a venous pH of 7.18, a peak venous lactate level of 6.4 mmol/L, and a BHB level of 4.7 mmol. Abdominal computed tomography showed mild hepatomegaly with fatty liver. Lactic acidosis syndrome secondarily to nucleoside analogues was diagnosed, antiretroviral therapy was discontinued, and intravenous fluids with bicarbonate were administered. The increased BHB level, however, was not consistent with this diagnosis. Review of the patient’s medications revealed that BHB acidosis can occur with isoniazid overdose (2). Treatment with intravenous pyridoxine (the only known antidote) was initiated (3). Eventually, therapy with oral bicarbonate, pyridoxine, L-carnitine, and B-complex vitamin was initiated, and the patient was discharged from the hospital. Although her acidosis subsequently resolved over the next 2 months, she did develop severe distal sensory polyneuropathy, possibly another manifestation of mitochondrial toxicity (4). She restarted highly active antiretroviral therapy that did not include a nucleoside analogue.

With the increasing complexity, longevity, and polypharmacy of HIV-infected patients, it is important to consider this potential drug “interaction” and complication of isoniazid.

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References