Inhaled Human Insulin for Type 2 Diabetes

Cefalu WT, Skyler JS, Kourides IA, et al. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. The Inhaled Insulin Study Group. Ann Intern Med 2001;134:203–7.

Study Overview

Objective. To determine the safety and efficacy of inhaled human insulin in patients with type 2 diabetes mellitus who require insulin.

Design. Prospective open-label, uncontrolled Phase I/II trial.

Setting and participants. 26 patients (16 men and 10 women) evaluated at a general clinical research center and outpatient research clinics (details not included in article). Participants met the following inclusion criteria: 35 to 65 years old, weight 100% to 175% of ideal body weight, on a stable insulin regimen (2 or 3 injections daily for 1 month or more), hemoglobin A_{1c} levels between 7.0% and 11.9%, and fasting C-peptide concentrations of 0.2 pmol/mL. Exclusion criteria were serum creatinine concentration 3.0 mg/dL or more, major comorbidities not directly related to diabetes (except hypertension), smoking within the past 6 months, current insulin pump therapy, receiving 4 or more doses of more than 150 U of insulin daily, and current oral hypoglycemic therapy.

Intervention. Patients were instructed to follow a weight maintenance diet, perform home glucose monitoring, and self-administer inhaled insulin. They received a preprandial dose of inhaled insulin with each meal as well as a bedtime dose of injected ultralente insulin. Target level for prandial plasma glucose was 100 to 160 mg/dL.

Main outcome measures. Change in hemoglobin A_{1c} levels, hypoglycemic events.

Main results. The average age of study subjects was 51.1 years; mean body mass index [BMI] was 30 kg/m² for men and 33 kg/m² for women. Hemoglobin A_{1c} levels showed a mean decrease of 0.7% (95% confidence interval [CI], –1.0% to –0.4%) over the 3-month treatment period. 69% of patients experienced mild to moderate hypoglycemic symptoms (average, 0.83 episodes per month), the majority of which occurred in the first 4 weeks of the study. No severe hypoglycemic events were recorded, and no pulmonary complications were noted.

Conclusion

Inhaled insulin is safe for short-term use in type 2 diabetic patients and appears to have some efficacy. However, this trial does not allow the efficacy of inhaled insulin versus standard parenteral insulin to be assessed.

Commentary

This study represents an early stage in the testing of inhaled insulin. Although Cefalu and colleagues seem to have demonstrated the treatment's efficacy, all that can be said for sure is that they have demonstrated short-term safety in a small group of patients. Efficacy is strongly suggested but cannot be ascertained without a control group.

An editorialist [1] has raised some concerns about the motivation driving the development of inhaled insulin—that is, facilitating the goal of achieving tight glucose control through several daily insulin doses. This author states that good management of type 2 diabetes is ultimately a question of how *much* insulin is given in a day, not of how *many* doses are delivered. Perhaps the most important issue here is maximizing effectiveness of therapeutic options rather than searching for the most efficacious agents. Most large clinical trials evaluate efficacy: patients are carefully selected and rigorously managed to isolate effects of the study intervention. In the real world, treatment efficacy is only one factor that determines patient outcomes. Eventually, *effectiveness* studies will be needed to compare different approaches to managing diabetes (as well as other common conditions). Such studies should focus on generalizability more than validity. (Validity is important to establish in *efficacy*-oriented studies.)

Applications for Clinical Practice

Patients with type 2 diabetes who wish to avoid multiple daily injections should be told that inhaled insulin requires substantial research before it can be considered for widespread use. These patients should be counseled that personal outcomes will largely be affected by their efforts and the efforts of their health care providers, regardless of what new technologies are developed in the foreseeable future.

References

1. Nathan DM. Inhaled insulin for type 2 diabetes: solution or distraction? Ann Intern Med 2001;134:242–3.