Inhaled insulin added to or replacing 2 oral agents reduced haemoglobin A$_{1c}$ concentrations in type 2 diabetes

Rosenstock J, Zinman B, Murphy LJ, *et al*. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 2005;**143**:549–58.

....

Q **Does inhaled insulin added to or replacing 2 oral agents reduce haemoglobin A$_{1c}$ (HbA$_{1c}$) concentrations in type 2 diabetes?**

METHODS

Design: randomised controlled trial.

Allocation: concealed.

Blinding: unblinded.

Follow up period: 12 weeks.

Setting: 48 outpatient centres in the US and Canada.

Patients: 309 outpatients 35–80 years of age (mean age 57 y, 65% men) who were diagnosed with type 2 diabetes ≥1 year earlier, were treated with a stable oral agent regimen of 2 antidiabetic medications (1 insulin secretagogue and 1 insulin sensitiser), and had HbA$_{1c}$ concentrations of 8–11%. Exclusion criteria were predisposition to severe hypoglycaemia; hospital admission or emergency department visit for poor diabetic control in the past 6 months; body mass index >35 kg/m^2; clinically significant respiratory disease or major organ system disease; smoking in the past 6 months; abnormal pulmonary function, electrocardiography, or laboratory result; systemic glucocorticoid therapy; substance abuse; previous inhaled insulin use; or pregnancy, lactation, or planned pregnancy.

Intervention: inhaled insulin (doses based on patient's weight and degree of glycaemic control and given within 10 min before meals) plus 2 oral agents (dual oral therapy) (n = 102); inhaled insulin monotherapy (n = 105); or dual oral therapy (n = 102).

Outcomes: change in HbA$_{1c}$ concentration. Secondary end points included changes in fasting plasma glucose and 2 hour postprandial glucose concentrations, acceptable (HbA$_{1c}$ <8%) or good (HbA$_{1c}$ <7%) glycaemic control, and hypoglycaemia.

Patient follow up: 96% included in intention to treat analysis.

....

For correspondence: Dr J Rosenstock, Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX, USA. juliorosenstock@dallasdiabetes.com

MAIN RESULTS

At 12 weeks, patients in each of the inhaled insulin groups had greater reductions in mean HbA$_{1c}$, fasting plasma glucose, and 2 hour postprandial glucose concentrations than patients in the dual oral therapy group. More patients achieved HbA$_{1c}$ concentrations <8% and <7% in the inhaled insulin plus dual oral therapy group and the inhaled insulin monotherapy group, respectively, than in the dual oral therapy group (table). The 2 inhaled insulin groups had higher rates of hypoglycaemia than the dual oral therapy group (table).

CONCLUSION

Inhaled insulin added to or replacing 2 oral agents reduced haemoglobin A$_{1c}$ concentrations in type 2 diabetes.

A modified version of this abstract appears in Evidence-Based Medicine.

Commentary

R educing the burden of daily diabetes management for patients is a concern for all practitioners. Achieving optimal glycaemic control in type 2 diabetes can be complicated by the progressive nature of the disease, warranting more treatment over time to minimise complications.[1] [2] Patients are often reluctant to move to insulin injections, perceiving them as punitive for failed attempts at diabetes management. Alternatives such as inhaled insulin are seductive because of their potential to improve patient acceptance of treatment options, but the need for clinical trials to establish their safety and effectiveness cannot be understated. Studies such as the one by Rosenstock *et al* are necessary before we can promote widespread use of inhaled insulin. The study met the minimum duration of 10 weeks needed for glycated haemoglobin to reliably reflect changes in glycaemic control.[3] It showed promising reductions in HbA$_{1c}$ concentrations, although these must be weighed against the consequences of the increased incidence of hypoglycaemia with the inhaled route. Clearly, longer follow up is needed to establish the safety of inhaled insulin in patients with compromised lung function and to identify long term side effects in the lung. The study by Rosenstock *et al*, however, moves us closer to alternative delivery routes for insulin administration.

Linda J Patrick, RN, PhD
Faculty of Nursing, University of Windsor
Windsor, Ontario, Canada

1 Stratton IM, Adler AI, Neil HA, *et al. BMJ* 2000;**321**:405–12.
2 Harris SB, Ekoé JM, Zdanowicz Y, *et al. Diabetes Res Clin Pract* 2005;**70**:90–7.
3 Royle P, Waugh N, McAuley L, *et al. Cochrane Database Syst Rev* 2003;(3):CD003890.

Inhaled insulin plus 2 oral agents (II2A) and inhaled insulin monotherapy (II) *v* 2 oral agents (2A) for type 2 diabetes*

Outcomes at 12 weeks	Comparison	Event rates	RBI (95% CI)	NNT (CI)
Haemoglobin A$_{1c}$ concentration <8%	II2A v 2A	86% v 19%	359% (207 to 609)	2 (2 to 2)
	II v 2A	56% v 19%	198% (93 to 372)	3 (3 to 5)
Haemoglobin A$_{1c}$ concentration <7%	II2A v 2A	32% v 1%	2972% (454 to 17536)	4 (3 to 5)
	II v 2A	17% v 1%	1500% (182 to 9260)	7 (5 to 12)
			RRI (CI)	**NNH (CI)**
Hypoglycaemia	II2A v 2A	78% v 8.3%	836% (396 to 1734)	2 (2 to 2)
	II v 2A	68% v 8.3%	712% (327 to 1498)	2 (2 to 3)

*Abbreviations defined in glossary; event rates, RBI, RRI, NNT, NNH, and CI calculated from data in article.