

Review: Inhaled insulin provides better glycemic control than oral hypoglycemic agents but not better than subcutaneous insulin

Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. *Ann Intern Med*. 2006;145:665-75.

Clinical impact ratings: Emergency Med ★★★★★☆ GIM/FP/GP ★★★★★☆ Allerg & Immunol ★★★★★☆☆ Pulmonology ★★★★★☆

QUESTION

In patients with diabetes, what is the relative efficacy, safety, and acceptability of inhaled insulin compared with subcutaneous (SC) insulin and oral hypoglycemic agents?

METHODS

Data sources: MEDLINE (to June 2006), Cochrane Controlled Clinical Trials Register (issue 2, 2006), reference lists, and the U.S. Food and Drug Administration Web site.

Study selection and assessment: Randomized controlled trials (RCTs) ≥ 12 weeks' duration, published as full, peer-reviewed, English-language articles that compared inhaled insulin with SC insulin or oral hypoglycemic agents in nonpregnant adult patients with type 1 or type 2 diabetes. 16 RCTs ($n = 4023$, mean age range 29 to 60 y, 58% men) met the selection criteria. Methodological quality was assessed based on randomization method, intention-to-treat analysis, dropout rate, and primary outcome (efficacy or safety).

Outcomes: Change in hemoglobin A_{1c} (HbA_{1c}) level, proportion of patients achieving HbA_{1c} level $< 7\%$, severe hypoglycemia, cough, change in pulmonary function, weight change, and patient satisfaction.

MAIN RESULTS

Inhaled insulin did not reduce HbA_{1c} level as much as SC insulin in patients with type 1 and type 2 diabetes but did reduce it more than oral agents in patients with type 2 diabetes (Table). The proportion of patients

who achieved HbA_{1c} levels $< 7\%$ or had ≥ 1 episode of severe hypoglycemia did not differ between inhaled and SC insulin but were higher with inhaled insulin than with oral agents (Table). Weight gain did not differ between inhaled and SC insulin (7 RCTs) but was higher with inhaled insulin than with combination oral therapy (3 RCTs). Risks for adverse pulmonary outcomes (cough and decrease in FEV₁ [15 RCTs]) were greater with inhaled insulin than with the other treatments. Patients with type 1 diabetes had a greater decrease in diffusing capacity of carbon monoxide with inhaled insulin than with SC insulin (6 RCTs).

Patient satisfaction was higher with inhaled insulin than with SC insulin (4 RCTs).

CONCLUSIONS

In patients with diabetes, inhaled insulin provides better glycemic control than oral hypoglycemic agents but not subcutaneous insulin. Inhaled insulin increases the risk for hypoglycemia more than do oral agents and the risk for pulmonary side effects more than do the other treatments.

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Inhaled insulin (II) vs subcutaneous (SC) insulin or oral hypoglycemic agents in diabetes at up to 24 weeks*

Outcomes	Number of trials (n)	Comparisons	Weighted mean difference (95% CI)		
Change in HbA _{1c}	11 (2620)	II vs SC	0.08% (0.03 to 0.14)†		
	6 (1499)	II vs oral agents	-1.04% (-1.59 to -0.49)‡		
			Event rates	RBI (CI)	NNT (CI)
HbA _{1c} $< 7\%$	5 (1016)	II vs SC	27% vs 25%	15% (-4 to 38)	Not significant
		II vs oral agents	31% vs 17%	87% (7 to 225)	7 (3 to 85)
			RRI (CI)	NNH (CI)	
Severe hypoglycemia	—	II vs SC	75% vs 78% (type 1) 16% vs 18% (type 2)	0% (-5 to 4)	Not significant
		II vs oral agents	9.4% vs 3.5%	206% (3 to 807)	14 (4 to 953)

*HbA_{1c} = hemoglobin A_{1c}. Other abbreviations defined in Glossary; RBI, RRI, NNT, NNH, and CI calculated from risk ratios and control event rates in article using a random-effects model.

†Favors SC.

‡Favors II.

COMMENTARY

As the arsenal of antidiabetes medications expands, insulin remains the most potent glucose-lowering agent available and is the only one for type 1 diabetes. Despite the large proportion of diabetic patients with suboptimally controlled blood sugar, relatively few take insulin (1), in part because of the perceived difficulty and pain of parenteral administration. Inhalation of insulin, if safe and efficacious, may be a more acceptable alternative to SC injection.

In the meta-analysis by Ceglia and colleagues, the difference in HbA_{1c} of 0.08% favoring SC over inhaled insulin is of uncertain clinical importance. Furthermore, the statistical significance of this difference may have been altered if techniques specific to meta-analysis of noninferiority studies had been used (2). The authors explained the heterogeneity among studies comparing inhaled insulin with oral agents, suggesting the benefits of inhaled insulin were less in longer-duration studies that allowed titration of oral medications in the control group.

Inhaled insulin may provide better short-term diabetes control than suboptimum use of oral agents, but it is not better than SC insulin. The short-term evidence of worse pulmonary function and symptoms and the unknown long-term risks associated with delivering an immunogenic growth factor in high concentrations to the lung warrant caution on the part of eager prescribers. The attractive feature of inhaled insulin is the apparent ease of administration. However, current devices may be considered large, cumbersome, and complicated to use, and long-term adherence may be an issue in clinical practice.

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References

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