Review: Long-acting insulin analogues reduce risk for hypoglycemia compared with NPH insulin in type 2 diabetes

Horvath K, Jeitler K, Berghold A, et al. **Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus.** Cochrane Database Syst Rev. 2007;(2):CD005613.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Endocrinology ★★★★★☆☆

QUESTION

In patients with type 2 diabetes mellitus, how effective and safe are long-acting insulin analogues compared with human isophane (NPH) insulin?

METHODS

Data sources: Cochrane Library, MEDLINE, EMBASE/Excerpta Medica, DARE, NHSEED, and HTA (to December 2006); online registries of clinical trials; Web sites of the European Medicines Agency and the U.S. Food and Drug Administration; reference lists; and pharmaceutical companies.

Study selection and assessment: Randomized controlled trials (RCTs) ≥ 24 weeks in duration that compared long-acting insulin analogues (insulin glargine or insulin detemir) with NPH insulin, given subcutaneously, in adults with type 2 diabetes. In the case of combination therapy, the additional antihyperglycemic agent had to be used in both treatment groups. 9 RCTs (n = 4193, mean age range 55 to 62 y, 40% to 64% men) with a median duration of 26 weeks (range 24 to 52 wk) met the selection criteria.

Outcomes: Incidence of overall, symptomatic, severe, and nocturnal hypoglycemia; and glycemic control (measured by hemoglobin A_{1c} [HbA_{1c}] level).

MAIN RESULTS

Glargine and NPH insulin did not differ for glycemic control: weighted mean difference in decrease in HbA_{1c} level was 0% (95% CI −0.10 to 0.09) (6 RCTs, n = 2902). NPH insulin reduced HbA_{1c} level by 0.12% (CI 0.01 to 0.23) more than detemir (2 RCTs, n = 967). Compared with NPH insulin, glargine reduced risks for symptomatic and nocturnal hypoglycemia, and detemir reduced risks for overall and nocturnal hypoglycemia (Table). Groups did not differ for severe hypoglycemia with either drug (Table).

CONCLUSION

In patients with type 2 diabetes, the long-acting insulin analogues glargine and detemir reduce risk for hypoglycemia compared with human isophane insulin, without sacrificing glycemic control.

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Long-acting insulin analogues vs human isophane (NPH) insulin for type 2 diabetes at 24 to 52 weeks*

Outcomes	Comparison	Number of trials (n)	Weighted event rates	RRR (95% CI)	NNT (CI)
Symptomatic hypoglycemia	Glargine vs NPH insulin	3 (1458)	53% vs 63%	16% (5 to 25)	10 (7 to 32)
Overall hypoglycemia	Detemir vs NPH insulin	2 (980)	58% vs 71%	18% (10 to 26)	8 (6 to 15)
Nocturnal hypoglycemia	Glargine vs NPH insulin	3 (1458)	25% vs 38%	34% (20 to 45)	8 (6 to 14)
	Detemir vs NPH insulin	2 (980)	25% vs 39%	37% (24 to 48)	7 (6 to 11)
Severe hypoglycemia	Glargine vs NPH insulin	4 (2207)	1.9% vs 2.7%	29% (–22 to 59)	Not significant
	Detemir vs NPH insulin	2 (980)	1.1% vs 2.2%	49% (–37 to 92)	Not significant

*Abbreviations defined in Glossary. RRR, NNT, and CI calculated from data in article using a random-effects model.

COMMENTARY

The proliferation of new insulin types over the past 10 to 15 years has been a welcome addition in the treatment of diabetes mellitus. For patients with type 1 diabetes, who have an absence of endogenous insulin, these newer agents help us to design insulin regimens that more closely mimic the action of a healthy pancreas by selecting combinations of immediate-acting insulins (e.g., aspart, lispro, and inhaled insulin), insulin pumps, and long-acting insulin analogues (e.g., glargine and detemir).

But which treatment is most effective for glycemic control in patients with type 2 diabetes, in whom some endogenous insulin secretion is generally preserved? These patients often respond initially to oral agents but later require the addition of insulin to achieve control. For this patient group, Horvath and colleagues systematically reviewed trials that assessed which insulin agents and regimens achieved good control while minimizing hypoglycemia. In many of these trials, such newer agents as glargine or detemir were compared with oral regimens taken during the day and the addition of NPH at night. Surprisingly, NPH did just as well as glargine and was slightly better than detemir in achieving glycemic control. This result is unexpected because NPH peaks at 4 to 6 hours and is gone by 12 hours, compared with a minimal peak and 24-hour duration for glargine.

The review by Horvath and colleagues can help us to work through the tradeoffs involved in choice of insulins. The main advantage of long-acting insulins for type 2 diabetes may be the decrease of reported hypoglycemia, but this is difficult to interpret based on the lack of blinding to treatment type and subjective definitions of hypoglycemia without additional objective confirmations (e.g., glucose levels or use of glucagon). "Relative hypoglycemia," that is, adrenergic but not neuroglycopenic symptoms at normal or even high glucose levels, is commonly reported in type 2 diabetes.

The disadvantages of long-acting insulin analogues include the cost, which is about twice that of NPH, and the fact that glargine cannot be mixed with short-acting insulins. This review suggests that we should reserve the newer insulin analogues for patients with type 2 diabetes in whom recurrent hypoglycemia on NPH has been documented by glucose measurements.

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