Review: Meglitinide analogues reduce glucose levels in type 2 diabetes, but morbidity and mortality effects are unknown

Black C, Donnelly P, McIntyre L, et al. **Meglitinide analogues for type 2 diabetes mellitus.** Cochrane Database Syst Rev. 2007;(2):CD004654.

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

QUESTION

In patients with type 2 diabetes mellitus (DM), are meglitinide analogues (MAs) effective and safe?

METHODS

Data sources: Cochrane Library (Issue 3, 2006); MEDLINE, EMBASE/Excerpta Medica, Science Citation Index, and ISI Proceedings (all to October 2006); an ongoing-trials database (www.controlled-trials.com); reference lists; meeting abstracts; and pharmaceutical companies.

Study selection and assessment: Randomized controlled trials (RCTs) that compared ≥ 10 weeks of an MA (repaglinide or nateglinide) with placebo or metformin or compared repaglinide with nateglinide alone or in combination with other oral agents or insulin in patients with type 2 DM. 15 RCTs (n = 3781) met the selection criteria. Follow-up ranged from 10 to 52 weeks (median 16 wk). Individual study quality was assessed by using the Schulz and Jadad scales and the manual of the Centre for Reviews and Dissemination for RCTs.

Outcomes: Mortality, diabetes-related complications, change in glycemic control from baseline (≥ 0.5% difference in glycosylated hemoglobin level [HbA_{1c}] was considered clinically significant), weight gain, episodes of symptomatic hypoglycemia, and diarrhea.

MAIN RESULTS

No trial reported on mortality or long-term complications of DM. The Table shows the results. Evidence for long-term safety and efficacy based on clinical outcomes is lacking.

CONCLUSION

In patients with type 2 diabetes mellitus, meglitinide analogues (especially repaglinide) reduce glucose levels, but morbidity and mortality effects are undocumented.

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Meglitinide analogues for type 2 diabetes at 10 to 52 weeks*

Comparisons	Number of trials (n)	Difference in change in HbA_{1c}†	Difference in change in weight (kg)‡	Hypoglycemia§	Diarrhea§
Rep vs plac	5 (987)	1.3% to 2.2% (4 RCTs) 0.42% to 0.55% (1 RCT)	1.5 to 2.9 (3 RCTs)	11% to 44% vs not reported	2% to 6% vs 0% to 1% (2 RCTs)
Rep + met vs met	1 (56)	1.1% (CI 0.4 to 1.7)‖	3.3 (CI 1.9 to 4.7)‖	33% vs 0%	19% vs 29%
Nat vs plac	4 (855)	0.4% to 1.0%	No difference	11% to 23% (2 RCTs) vs 5% (1 RCT)	2.8% vs 5.2% (1 RCT)
Nat + met vs met	2 (815)	0.4%; 0.6%	0.3 0.9 (CI 0.4 to 1.5)‖	26% vs 10%‖¶ 12% vs 3.9%‖¶	15% vs 20% 5.6% to 5.8% vs 8%
Rep vs nat	1 (150)	0.5% (CI 0.1 to 0.9)‖	1.1	0% vs 0%	Not reported
Rep + met vs nat + met	1 (192)	0.6% (CI 0.3 to 0.9)‖	1.1	7% vs 2%	No difference
Rep vs met	2 (168)	–0.1%; 0.1%	1.2; 3.8 (CI 2.5 to 5.2)‖	11% vs 0% (1 RCT)	7% vs 30% (1 RCT)‖
Rep + insulin vs met + insulin	1 (80)	–0.8%	1.8 (CI 0.7 to 2.9)§	0% vs 0%	Not reported
Nat vs met	1 (355)	–0.3%	No difference	13% vs 10%¶	5% to 7% vs 20%‖

*HbA_{1c} = glycosylated hemoglobin; met = metformin; nat = nateglinide; plac = placebo; rep = repaglinide. CI defined in Glossary.
†Positive value indicates greater reduction in HbA_{1c} in the first group compared with the second group; negative value indicates less reduction.
‡Positive value indicates greater weight increase in the first group compared with the second group.
§Proportion of patients with hypoglycemia or diarrhea in the first group compared with the second group.
‖Statistically significant difference between groups.
¶Hypoglycemic episode rate (episodes reported/number of patients in group).

COMMENTARY

The well-conducted review by Black and colleagues summarized current information on the efficacy and safety of MAs, which are insulin secretagogues, in the treatment of type 2 DM. The review highlighted several important issues. First, starting at similar HbA_{1c} levels at baseline, both MAs improved glycemic control, but repaglinide provided greater mean HbA_{1c} reductions than nateglinide, compared with placebo or in combination with metformin. In a head-to-head comparison starting at similar baseline levels, more patients achieved HbA_{1c} levels < 7% with repaglinide + metformin than nateglinide + metformin (59% vs 46%) (P = 0.06)**. Second, no existing studies compared the efficacy of MAs and sulfonylureas (SUs) or thiazolidinediones (TZDs). Third, no data exist on the long-term effects of MA on morbidity and mortality. In the RCTs reviewed by Black and colleagues, the median duration of MA treatment was only 16 weeks. Long-term safety is an important concern, further heightened by the ongoing controversy about TZDs, for which favorable effects on a surrogate measure (HbA_{1c}) are counterbalanced by increases in congestive heart failure and, perhaps, cardiovascular mortality (1, 2). Fourth, this review provides no insight into the theoretical advantage of MAs over such traditional SUs as glyburide.

Clinicians may wish to read a recent review of oral hypoglycemic agents by the Agency for Healthcare Research and Quality (3). Neither review provides a compelling reason to use MAs routinely for patients with type 2 DM.

**Calculated from data in article.

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