Repaglinide and gemfibrozil interaction: serious hypoglycemia

Repaglinide (GlucoNorm) is a short-acting, orally administered drug used to manage postprandial hyperglycemia in type 2 diabetics. Although chemically unrelated to sulfonylureas, it stimulates insulin secretion from pancreatic β-cells. Repaglinide's level peaks within an hour after ingestion, and the drug has a half-life of about an hour. The drug is metabolized in part by the cytochrome P450 (CYP) system (3A4 and 2C8 enzymes) and is excreted mostly fecally.[1,2] Hypoglycemia, a known adverse effect of the drug, is more common in patients who have skipped meals or have hepatic, pituitary or adrenal insufficiency, or those taking β-blockers, ketoconazole, miconazole or erythromycin.[1]

Gemfibrozil is a fibrate drug commonly used in patients with type 2 diabetes[3] and inhibits CYP2C8.[2] Because of a concern about a possible CYP interaction, Niemi and colleagues[2] recently studied healthy volunteers given both gemfibrozil (600 mg twice daily) and repaglinide (0.25 mg once daily). They found that the half-life of repaglinide was significantly prolonged (from 1.3 to 3.7 hours, $p < 0.001$) and that the drug's glucose-lowering effect was significantly enhanced and prolonged.

In light of this potentially serious interaction, repaglinide's product monograph will be revised to indicate the increased risk of severe and prolonged hypoglycemic reactions in patients taking this combination of drugs.[4] The combination is now considered contraindicated, and alternative treatment should be considered for any patient taking both drugs. Five serious reports of hypoglycemia in patients taking both repaglinide and gemfibrozil have been reported worldwide, but no cases have been reported to date in Canada.[4]

Risk of death in patients with localized prostate cancer taking bicalutamide (Casodex)

Bicalutamide (Casodex) is a nonsteroidal anti-androgen used to block testosterone's promotion of prostate cancer growth. In November 2002 Health Canada granted a Notice of Compliance with Conditions that allowed patients with localized prostate cancer who were not candidates for radiation therapy or surgery to be given bicalutamide at a dose of 150 mg once daily. However, a recent letter to health care professionals warns that data pooled from 3 recent double-blind randomized controlled trials show that the drug may increase the risk of death.[5]

The 3 trials involved a total of 8113 patients with localized prostate cancer or locally advanced but not metastatic prostate cancer. (Health Canada has not approved Casodex 150 mg for the treatment of locally advanced disease.) The men received bicalutamide (150 mg) or placebo, either as adjuvant therapy to their primary treatment (radical prostatectomy or radiation therapy) or as immediate treatment if they were being managed with "watchful waiting" (patients for whom surgery or radiation therapy, as a primary treatment, would be inappropriate). After a median follow-up of 5.4 years overall, the men given the drug had a significant reduction in the risk of disease progression compared with those given placebo (hazard ratio [HR] 0.73, $p < 0.001$). This benefit was greatest in both the adjuvant and watchful-waiting settings for men with a high risk of disease progression (those with locally advanced disease, a high prostate-specific antigen level or a high Gleason score).

However, in the watchful-waiting subgroup, after the median follow-up of 5.4 years, the rate of death was higher in the treatment group than in the placebo group (25.2% v. 20.5%; HR 1.23, 95% confidence interval 1.00–1.50). The risk of death was highest among men with the least severe disease. It is thus recommended that clinicians discontinue prescribing bicalutamide 150 mg once daily for patients with localized prostate cancer. This warning does not apply to using the 50 mg dose for the treatment of metastatic prostate cancer.

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References

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