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EDITORIAL: A NEED FOR GLUCOSE MONITORING ON PROKINETIC TREATMENT WITH A GHRELIN AGONIST IN DIABETIC GASTROPARESIS?

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Prokinetics that accelerate delayed gastric emptying are mainstays of gastroparesis therapy. Only metoclopramide was approved by the U.S. Food and Drug Administration for gastroparesis over 40 years ago. Because of the largely non-fatal nature of symptoms, much of the focus on gastroparesis therapy has been on safety of prokinetics. Metoclopramide prescriptions for patients with gastroparesis have decreased from 69.8% to 23.7% due to concerns about tardive dyskinesia (1). Case-control studies documenting increased sudden cardiac deaths led to 40-70% reductions in domperidone prescriptions (2).

Relamorelin is a promising ghrelin agonist that significantly improved symptoms in phase 2a and 2b trials in diabetic gastroparesis. Camilleri and colleagues have highlighted the critical topic of its safety (3). There were no major cardiovascular complications apart from unstable angina in some diabetics with pre-existing vascular disease.

Hyperglycaemia warrants special consideration in any indication for diabetics. The authors comment that this is a risk with any prokinetic; whenever food is emptied quickly into the intestine, glucose levels can increase. This has been documented for some but not all prokinetics. In the hour after intravenous erythromycin, postprandial glycaemia peaks 50 mg/dL higher than after placebo in type 2 diabetics. However, cumulative 5-hour glucose increases after meals are not increased by erythromycin consistent with a prokinetic effect and no additional metabolic mechanisms (4). Erythromycin, the most potent gastrokinetic, accelerates 2-hour gastric emptying from 37±9% to 96±1% in gastroparesis patients with type 1 diabetes (5). Conversely, weaker prokinetics including cisapride do not impact glycaemic control (6).

Hyperglycaemia after relamorelin probably stems from combined prokinetic, appetite, and metabolic effects. Parenteral relamorelin is a potent gastrokinetic promoting 25% greater 2-hour gastric emptying than placebo in type 2 diabetics (7). No postprandial glycaemic data were provided in this paper but fasting glucose increased in a dose-related fashion up to 1.74 mmol/L (31 mg/dL) higher than with placebo, and glycosylated haemoglobin increased 0.8-0.9% on higher relamorelin doses. Whereas erythromycin increases insulin levels in the first postprandial hour after rapid intestinal carbohydrate delivery, native ghrelin and other ghrelin agonists (*e.g.*, ulimorelin) inhibit insulin release for up to 4 hours contributing to hyperglycaemia (4, 8, 9).

The relamorelin data are encouraging in that significant glycaemic complications presented only in small numbers of patients. Nine patients (1.5%) discontinued study participation because of glucose control. Four patients experienced ketoacidosis deemed unrelated to relamorelin. However, these trials were not designed to monitor glycaemia and no glucose levels were pre-defined to constitute adverse events. Proactive glucose monitoring is ongoing in phase 3 relamorelin trials in diabetic gastroparesis, which will only test the lowest dose from the phase 2b study (10 µg twice daily) thereby limiting the risk of hyperglycaemia. This dedicated approach may have the added benefit of improving clinical responses to relamorelin as prokinetic actions of other drugs like erythromycin are blunted by mild hyperglycaemia (10). If approved for diabetic gastroparesis, post-marketing surveillance and the prescription marketplace will determine the long-term impact of relamorelin-induced hyperglycaemia.

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