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Editorial: a need for glucose monitoring on prokinetic treatment with a ghrelin agonist in diabetic gastroparesis?

Prokinetics that accelerate delayed gastric emptying are mainstays of gastroparesis therapy. Only metoclopramide was approved by the US 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 *et al* 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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LINKED CONTENT

This article is linked to Camilleri et al and Camilleri papers. To view these articles, visit https://doi.org/10.1111/apt.15711 and https://doi.org/10.1111/apt.15866.

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Editorial: a need for glucose monitoring on prokinetic treatment with a ghrelin agonist in diabetic gastroparesis? Author's reply

We thank Dr Hasler for the excellent discussion points that he raised in the editorial relating to our article on the safety of relamorelin in adult patients with diabetic gastroparesis.[1,2]

We agree with the general principle that a combination of the prokinetic, appetite-stimulating and metabolic effects of ghrelin agonists is likely to be responsible for hyperglycaemia observed with relamorelin. We also agree that the relamorelin data are encouraging given that glycaemic complications presented in a relatively small number of patients, with only 1.5% across phase 2a and 2b trials discontinuing participation due to issues related to glycaemic control. We acknowledge that less potent prokinetics may not significantly affect glycaemic control; cisapride, for example, was not associated with significant glycaemic disturbances over a 28-day period.[3]

However, the literature indicates that the rate of gastric emptying is a major determinant of both early and overall postprandial glycaemia,[4] and faster gastric emptying (induced by erythromycin) was associated with greater postprandial glucose measurements in 30 patients with type 1 diabetes mellitus treated with an insulin pump.[5] Moreover, after adjusting for carbohydrate intake and insulin consumption, faster gastric emptying was associated with increased postprandial hyperglycaemia but lower glucose values across the study overall.[5]

Dr Hasler cited an article by the group at Temple University, which showed that cumulative 5-hour blood glucose increases after meals are not increased by erythromycin, in contrast to the first postprandial hour where hyperglycaemia was observed.[6] It is worth noting that prokinetic effects are generally most apparent in the first postprandial hour, and that cumulative 5-hour data largely reflect the absorptive capacity of the small intestine rather than gastric emptying. The findings of that study confirm that the rate of gastric emptying particularly impacts on early postprandial glycaemia. Indeed, the increase in insulin in the first postprandial hour is an expected response to glycaemia in a population of patients with type 2 diabetes mellitus.

In the Discussion section of our article, we also identified that the metabolic effects of ghrelin agonists are potentially relevant to the development of hyperglycaemia. Our overall objective was similar to that of Dr Hasler: we wished to draw attention to the risk of hyperglycaemia with such an effective prokinetic as relamorelin and stress the importance of proactive glycaemic management (as should be the goal for all diabetic patients) during the phase 3 trials and potentially in clinical practice in the future.

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