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Effect of lixisenatide on liquid gastric emptying in type 2 diabetes – Implications for the use of GLP-1 receptor agonists before procedures

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A B S T R A C T

Gastric emptying of a glucose drink was measured in people with type 2 diabetes given lixisenatide (20 μg/day or placebo) for 8 weeks. Intragastric retention at 240 min (2 (0−11)% vs 48 (3–97)%; $P < 0.0001$) was much greater with lixisenatide than placebo. Accordingly, lixisenatide may delay liquid gastric emptying markedly.

1. Introduction

The American Society of Anesthesiologists (ASA) recently published guidance relating to the use of glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) before procedures, based mainly on anecdotal reports of retained gastric contents despite apparently appropriate periods of fasting.[1] These state that short-acting (once or twice daily dosing) agents should be held on the day of procedure, while longer-acting (weekly dosing) be held one week prior,[2] and consideration given to point of care ultrasound to quantify gastric residue. There is a lack of consensus regarding a gastric volume that confers a meaningful increase in aspiration risk, but it may be as low as 30 mL.[3,4] Moreover, a less restrictive period of pre-procedure fasting is increasingly advocated, with the recent guidance recommending ingestion of carbohydrate-containing clear fluids until two hours preoperatively.[5] This is despite the recognition that gastric emptying of nutrient liquids and solids are comparable after the initial solid lag phase, at a rate of 1–4 kcal/min in health.[6] For individuals with diabetes, who frequently have disordered (both delayed and accelerated) gastric emptying,[6] an increased aspiration risk is recognised, and clinical judgment is advised, rather than the two-hour fasting window.[5,7]

To better characterise the effect of the short-acting GLP-1RA, lixisenatide, to slow gastric emptying, we conducted a further analysis in patients with type 2 diabetes given lixisenatide or placebo for 8 weeks.[8]

2. Materials and methods

Data were extracted from the dataset of a double-blinded, randomised trial in which 30 participants with type 2 diabetes, treated with metformin, were randomised to eight weeks' treatment with either 20 μg lixisenatide or placebo (saline) (15 subjects in each group).[8] Measurement of gastric emptying (scintigraphy) of a 300 mL, 75 g glucose drink (i.e. 25 % glucose) radiolabeled with 20 MBq ^{99m}Tc-calcium phytate was performed before and with treatment. Scintigraphic data were acquired for 240 min following the drink.[9]

The intragastric retention of the drink at 120 and 240 min was calculated and data analysed using an unpaired Mann-Whitney *U* test; a *P* value <0.05 was considered significant. Gastric emptying curves in the lixisenatide cohort were extrapolated, using a polynomial curve fit (Microsoft® Excel for Mac, Microsoft 365, V16.85, Redmond, WA, USA) to calculate the time to 10 % (30 mL) intragastric retention. Demographic data are presented as mean values ± SEM. Gastric emptying data are presented as median and ranges. The study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, and prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12616001059459).

3. Results

In the lixisenatide cohort ($n = 15$), 10 (67 %) were male, aged 67.1 ± 6.2 years, body mass index 32.0 ± 4.1 kg/m^2, and glycated hemoglobin (HbA1c) 6.9 ± 0.4 % (52 ± 4.4 mmol.mol^{-1}) and in the placebo

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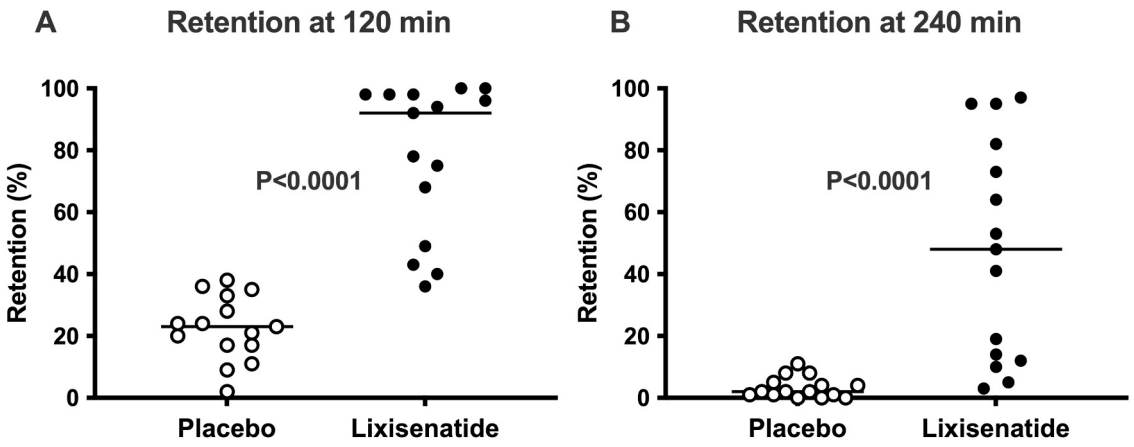

Fig. 1. Intragastric retention of a 300 mL drink containing 75 g glucose at (A) 120 min and (B) 240 min after ingestion in 30 participants with type 2 diabetes after 8 weeks treatment with either lixisenatide ($n = 15$) or placebo (n = 15). Median values are indicated.

cohort (n = 15), 11 (73 %) were male, age 67.2 ± 5.9 years, body mass index 32.1 ± 6.1 kg/m^2, HbA1c 7.3 ± 0.6 % (56 ± 6.6 mmol.mol^{-1}), before treatment.[8]

Intragastric retentions [median (range)] at 120 min (placebo: 23 (2–38)% vs lixisenatide: 92 (36–100)%; $P < 0.0001$) and 240 min (placebo: 2 (0–11)% vs lixisenatide: 48 (3–97)%; $P < 0.0001$) were much greater with lixisenatide (Fig. 1). Curve fitting was not possible in two participants following lixisenatide treatment as the delay in gastric emptying was profound. In these two participants it was assumed that 10 % gastric retention was greater than the other 13 participants, hence, the median time to 10 % gastric retention for $n = 15$ participants was 307 (204 – >880) min.

4. Discussion

Our analysis establishes that in metformin-treated type 2 diabetes treated with lixisenatide for 8 weeks, gastric emptying of a high-nutrient liquid may be delayed markedly - a median of 276 mL of a 300 mL carbohydrate drink remained in the stomach at two hours, and 144 mL at four hours, and the median time to 10 % intragastric retention was >300 min.

Scintigraphy remains the 'gold-standard' technique for measurement of gastric emptying.[7] 'Short-acting' – and more recently, contrary to expectation, 'longer-acting' GLP-1RAs have been shown to have a durable and substantial effect to slow gastric emptying, of relevance to postprandial glucose lowering and weight loss.[10–13] In obese individuals liraglutide (3 mg sc/da) has been shown to lead to a persistent delay in gastric emptying in 30 % at 16 weeks.[14] Lixisenatide has also been shown, using scintigraphy, to affect intragastric distribution of a 25 % glucose drink and this is likely to occur with other GLP-1RAs.[15] This is not surprising, given that GLP-1 is known to affect the motor function of the proximal and distal stomach.[16] There is a lack of reliable information relating to the effect of individual GLP-1RAs on gastric emptying and the latter has often been evaluated using suboptimal methodology.[7]

The recent guidance relating to cessation of GLP-1RAs before elective procedures is precautionary and the evidence base is primarily anecdotal.[2] Retained gastric contents at upper gastrointestinal endoscopy are not unusual in diabetes, nor pathognomonic of gastroparesis.[17] Short-acting GLP-1RAs slow gastric emptying markedly in doses that are substantially less than those used for glucose lowering.[9,18] This is not surprising, given that GLP-1 plays a physiological role to slow gastric emptying.[19] Accordingly, omitting a short-acting GLP-1RA for 24 h may well not prevent marked delay in gastric emptying and fasting for 2–4 h is almost certainly insufficient given that the time to 10 % retention (30 mL) was ~5 h. For a short-acting GLP-1RA, a period of cessation of in excess of 2 days may be required. It is likely that the effect of long-acting GLP-1RAs to slow gastric emptying also occurs in lower doses than used clinically, although, tachyphylaxis to the slowing of gastric emptying is evident in some individuals.[11] With both 'short'- and 'long'-acting GLP-1RAs, slowing of gastric emptying is greatest when the baseline rate of gastric emptying is faster,[18] suggesting that individuals with gastroparesis may be at less risk. Accordingly, the recent ASA statement advising withholding long-acting agents for a week before a procedure[2] is likely to be insufficient to prevent gastroparesis, given that plasma drug levels are identifiable at that time. In the population we studied (uncomplicated type 2 diabetes), gastric emptying is more likely to be accelerated, rather than delayed,[6] as is the case in obese individuals without diabetes.[20] These considerations highlight the urgency for further research, including the requirement for measurement of gastric emptying using a sensitive technique in the pre-marketing evaluation of GLP-1RAs.[20]

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CRediT authorship contribution statement

Joshua G. Kovoor: Writing – original draft, Investigation, Formal analysis. **Christopher K. Rayner:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Tongzhi Wu:** Writing – review & editing, Investigation. **Ryan J. Jalleh:** Writing – review & editing, Investigation. **Guy J. Maddern:** Writing – review & editing, Supervision, Investigation. **Michael Horowitz:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Karen L. Jones:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

This manuscript represents a secondary analysis of our published randomised clinical trial (RCT) evaluating the effect of chronic (8 week) treatment with the short-acting glucagon-like peptide-1 (GLP-1) receptor agonist, lixisenatide on gastric emptying, using the gold standard technique, scintigraphy, and glucose metabolism in people with type 2 diabetes (Rayner et al. Diabetes Care 2020;43:1813–1821). An erratum of the original paper was subsequently published (Rayner et al. Diabetes Care 2021;44:297) correcting some minor errors unrelated to this submission.

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Gastric emptying data, expressed as gastric emptying curves (mean data ± SD), has been published previously (ref [9]). In contrast, individual data is illustrated in this manuscript, along with further analysis to extrapolate the curves using a curve fit analysis. Scintigraphic data was acquired on a 100 % research-dedicated gamma camera (Siemens eCam, kindly donated by Radiology SA). K.L.J. is the guarantor of this secondary work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the secondary data analysis.

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