The Effect of Exogenous Glucose-Dependent Insulinotropic Polypeptide in Combination With Glucagon-Like Peptide-1 on Glycemia in the Critically Ill

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OBJECTIVE—Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) have additive insulinotropic effects when coadministered in health. We aimed to determine whether GIP confers additional glucose-lowering to that of GLP-1 in the critically ill.

RESEARCH DESIGN AND METHODS—Twenty mechanically ventilated critically ill patients without known diabetes were studied in a prospective, randomized, double-blind, crossover fashion on 2 consecutive days. Between T0 and T420 minutes, GLP-1 (1.2 pmol/kg min−1) was infused intravenously with either GIP (2 pmol/kg min−1) or 0.9% saline. Between T60 and T420 minutes, nutrient liquid was infused into the small intestine at 1.5 kcal/min.

RESULTS—Adding GIP did not alter blood glucose or insulin responses to small intestinal nutrient. GIP increased glucagon concentrations slightly before nutrient delivery (P = 0.03), but not thereafter.

CONCLUSIONS—The addition of GIP to GLP-1 does not result in additional glucose-lowering or insulinotropic effects in critically ill patients with acute-onset hyperglycemia.

Hyperglycemia occurs frequently in the critically ill, even in the absence of pre-existing diabetes (1). Although insulin is an effective treatment, its use confers an increased risk of hypoglycemia, which is associated with increased mortality (1,2). In health, but not in patients with type 2 diabetes, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) have additive insulinotropic effects when coadministered, without increasing the risk of hypoglycemia (3,4). The objective of this study was to determine whether the addition of GIP to GLP-1 would result in additional glucose-lowering in enterally fed, critically ill patients without pre-existing diabetes.

Data analysis
Blood glucose concentrations were measured immediately using a blood gas analyzer (ABL800 FLEX; Radiometer). Serum insulin was measured by ELISA, while plasma glucagon, GIP, and GLP-1 were measured using radioimmunoassays.

Statistical analysis
Based on previous data, 20 completed subjects were required (5). Data are presented as mean ± SD or median (range) as appropriate. As data for inferential analysis were normally distributed, comparisons were made using the Student paired t test. Because the islet cell effects of GIP are glucose-dependent (6,7), the effect of GIP in the subgroup of patients in whom peak blood glucose concentrations were >10 mmol/L was also assessed.

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RESULTS—Twenty patients (age 52 ± 16 years; sex: 12 male; HbA1c: 5.7% [range 4.8–6.5%], 39 [29–48] mmol/mol; Acute Physiology and Chronic Health Evaluation II score: 17 [9–30]; days in ICU when studied: 6 [2–15]; admission diagnostic group: sepsis, 9; trauma, 7; asthma, 2; neurological, 2) were studied.

Blood glucose
Baseline blood glucose concentrations were similar on both days (P = 0.38). In nine patients, the peak blood glucose was >10 mmol/L at least on one study day. GIP had no effect on fasting, peak, or overall glycemic response in either the entire cohort (Fig. 1A) or the group with glycemic excursions >10 mmol/L (Fig. 1B).

Insulin
Baseline insulin concentrations were similar on the 2 days (P = 0.81). GIP had no effect on fasting or overall insulin concentrations in either the entire cohort (Fig. 1C) or the subgroup of patients with glycemic excursions >10 mmol/L (P = 0.96).

Glucagon
Baseline glucagon concentrations were similar on the 2 days (P = 0.48). The addition of GIP led to a minor increase in glucagon before nutrient was given (T60: 152 ± 93 vs. 145 ± 113 pg/mL; P = 0.03), but there was no difference at the end of the infusion (P = 0.55). Overall, glucagon responses to the infusion were also comparable regardless of GIP administration (Fig. 1D). There was no difference in the glucagon response between the 2 days in patients with glycemic excursions >10 mmol/L (P = 0.38).

GIP and GLP-1
Baseline GIP and GLP-1 concentrations were similar on both days (P = 0.79 and 0.35, respectively). While there was a sustained twofold rise above fasting plasma GIP concentrations in response to intraduodenal nutrient during the control infusion (P < 0.001), GIP concentrations were fourfold greater during GIP infusion (P < 0.001). On both days, GLP-1 concentrations increased ~40% in response to GLP-1 infusions, with the addition of GIP having no effect on plasma GLP-1 concentrations (P = 0.88).

CONCLUSIONS—This study indicates that IV administration of GIP to
GLP-1 does not lower blood glucose concentrations in the critically ill more than exogenous GLP-1 alone. In keeping with this, the addition of GIP does not affect insulin or suppress glucagon response to enteral nutrient. While these observations are at variance with the outcome of studies performed in healthy volunteers (3,4), they are consistent with the reported effects of concurrent administration of GLP-1 and GIP in patients with type 2 diabetes (4,8).

The doses of GIP and GLP-1 used were based on previous studies. We have reported that GLP-1 at 1.2 pmol/kg • min⁻¹ attenuates, but does not abolish, the glycemic response to enteral nutrition in critically ill patients with and without type 2 diabetes (5,9,10). While this is the first report on the effects of GIP in the critically ill, in healthy volunteers, the co-infusion of GIP at doses >1 pmol/kg • min⁻¹ is additive to the insulinoergic effect of GLP-1 (3,4). We confirmed that GIP concentrations reached pharmacological levels, so it appears unlikely that the negative outcome of our study reflects an insufficient dose of GIP.

The reason GIP failed to lower glucose concentrations may relate to antecedent glycemic control, as the insulinoergic effect of GIP is markedly attenuated in various conditions associated with chronic hyperglycemia, such as latent autoimmune diabetes, chronic pancreatitis, and monogenic diabetes (11,12). Moreover, in vivo, hyperglycemia acutely reduces the expression of GIP receptors on β-cells, providing a plausible explanation as to why even pharmacological concentrations of GIP are not insulinoergic during chronic hyperglycemia (13). Højberg et al. (14) recently reported that the insulinoergic property of GIP increased sevenfold following 4 weeks of near-normal glycemia in patients with type 2 diabetes. These data and ours indicate that the response of the β-cell to pharmacological doses of GIP is acutely susceptible to the effects of antecedent glycemia. In both healthy humans and patients with pre-existing hyperglycemia and hyperglucagonemia, exogenous GIP is reportedly glucagonotropic, which would counteract any insulinoergic effect (6,8,11,15). However, we observed a modest glucagonotropic effect during fasting (T₆₀), which is unlikely to be of clinical significance.

There are limitations to our study. We cannot exclude the possibility that GIP alone lowers glycemia in the critically ill compared with placebo. Our cohort was relatively small and heterogeneous, and the exposure to exogenous GIP was relatively short (7 h). It therefore remains possible, albeit intuitively unlikely, that an insulinoergic effect would be apparent during more prolonged GIP exposure.

In conclusion, this study indicates that the addition of GIP to exogenous GLP-1 does not yield any additional glucose-lowering effect, nor potentiate insulin secretion, in critically ill patients. The implication is that the insulinoergic capacity of GIP, unlike GLP-1, is diminished in critically ill patients with hyperglycemia, as is the case in patients with type 2 diabetes.

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No other potential conflicts of interest relevant to this article were reported.

M.Y.L. was responsible for acquisition of data, statistical analysis, and drafting the manuscript. J.D.F. and K.S. contributed to subject enrollment. M.J.C., C.K.R., J.J.M., and M.H. contributed to the study design and critical revision of the manuscript for important intellectual content. M.M.U., M.J.S., and A.V.Z. contributed to the acquisition of data. A.M.D. was responsible for the study conception and design, obtaining funding, acquisition of data, interpretation, and manuscript review. A.M.D. is the guarantor of this 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 data analysis.

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