Commentary

Incretins in the ICU: is insulin on its way out?

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Published: 2 July 2009
This article is online at http://ccforum.com/content/13/4/161

Critical Care 2009, **13:**161 (doi:10.1186/cc7913)

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Abstract

Incretins such as glucagon-like peptide-1 (GLP-1) are gut-derived hormones that stimulate insulin secretion and suppress glucagon secretion, thus playing a key role in glucose homeostasis. While incretin mimetics and enhancers are approved for treatment of outpatients with diabetes, evidence is only starting to accumulate regarding the therapeutic potential of incretins in hospitalized patients. Small exploratory studies suggest that GLP-1 safely reduces hyperglycemia without causing hypoglycemia, a key advantage over insulin if efficacy is established in larger studies. Potential limitations include the need for a continuous infusion for delivery, attenuation but not normalization of glucose levels, increased deceleration of gastric emptying and nausea. The exact mechanism of action, dosing, adverse effects, patient subgroups that would be most suitable and safety of combination treatment with insulin remain to be studied. While promising, additional research is required studying effects on hard clinical endpoints.

Treatment with insulin in hospitalized patients, while effective, is resource intensive and associated with hypoglycemia. In a small proof-of-concept study published in the present issue of *Critical Care*, Deane and colleagues report on a novel therapeutic agent to treat hyperglycemia in critically ill patients [1]. They evaluated the effects of the incretin hormone glucagon-like peptide-1 (GLP-1) compared with placebo on seven mechanically ventilated patients without diabetes receiving enteral nutrition in a mechanistic randomized blinded crossover study. GLP-1 caused a significant reduction in peak blood glucose compared with placebo (231 mg/dl vs. 184 mg/dl) without causing hypoglycemia. The response was mediated by increased insulin secretion and a transient nonsustained decrease in glucagon concentrations. So why should intensivists take notice?

Nutritional support via the enteral route is frequently utilized in hospitalized patients, especially in the critically ill who are in a catabolic state, and is generally preferred over parenteral nutrition [2]. Hyperglycemia is frequently seen in this critically ill patient population, even in those without known diabetes [3,4]. To date insulin therapy (usually intravenous infusion in intensive care units and subcutaneous injections in general medicine–surgery wards) has been the intervention used to most quickly and effectively control glucose levels in this setting. There is currently limited evidence-based data from small studies [3,5] to guide which type, which route or which regimen of insulin should be used. It would be ideal to have a noninsulin option for treating hyperglycemia that would reduce the incidence of hypoglycemia and would possibly be less labor intensive.

Enter incretin therapy. The search for incretin hormones began when it was shown that oral glucose administration significantly increased insulin secretion compared with isoglycemic intravenous glucose challenge, suggesting that gut hormones had a role in signaling insulin release [6]. Two enteroendocrine hormones have been found with this insulinotropic action: GLP-1 released from L cells in the distal ileum and colon, and gastric inhibitory polypeptide released from the proximal small bowel.

Patients with type 2 diabetes have a reduced incretin effect [7]. Pharmacologic therapy with degradation-resistant GLP-1 receptor agonists (incretin mimetics) and inhibitors of dipeptidyl peptidase-4, the enzyme that degrades GLP-1 (incretin enhancers), has been used to improve glycemia in the outpatient setting. Administering exogenous gastric inhibitory peptide, even at supraphysiologic doses, does not increase insulin levels with little or no change in glucose levels. On the other hand, GLP-1 administration increases insulin secretion to normal levels and lowers plasma glucose levels effectively [8]. Other known beneficial effects of GLP-1 include slowing gastric emptying (which reduces excessive postprandial glucose excursions), suppression of glucagon (a counter-regulatory hormone), an increase in pancreatic islet β-cell mass, suppression of appetite and induction of satiety [8-12]. The beauty of GLP-1 is that it does not stimulate

GLP-1 = glucagon-like peptide-1.

Table 1

Summary of studies on glucagon-like peptide-1 in hospitalized patients

	Deane and colleagues [1]	Mussig and colleagues [14]	Sokos and colleagues [15]	Meier and colleagues [16]
Patient population	ICU, mechanically ventilated	Post CABG	Pre and post CABG	Post major surgery
Number of patients	7	20	20	8
Male/female	4/3	18/2	17/3	5/3
Diabetes mellitus	No	All	5/20	All
Nutrition	Enteral feeding	No parenteral feeding	Allowed to eat	Fasting
Intervention	GLP-1 at 1.2 pmol/kg/minute	GLP-1 at 3.6 pmol/kg/minute	GLP-1 at 1.5 pmol/kg/minute	GLP-1 at 1.2 pmol/kg/minute
Duration of intervention	4.5 hours	12 hours	12 hours before CABG to 48 hours after CABG	8 hours
Control group	Placebo (albumin)	Insulin	Placebo (saline)	Placebo
Results	Significantly decreased AUC for glucose	Glycemic control comparable with insulin-treated group	Significantly decreased AUC for glucose	Normoglycemia
Side effects	None	None	One episode of hypoglycemia	None

AUC, area under the curve; CABG, coronary artery bypass grafting; GLP-1, glucagon-like peptide-1; ICU, intensive care unit.

insulin secretion in euglycemic ranges, thus potentially eliminating the risk of hypoglycemia – making GLP-1 a very attractive pharmacologic option for treating hyperglycemia in hospitalized patients.

GLP-1 may indeed have a variety of exciting therapeutic applications as evidence starts to accumulate in inpatients (Table 1). Results suggest that hyperglycemia in varied hospital settings (post surgery, critical illness, enteral feeding) in diabetic and nondiabetic patients may be alleviated with use of GLP-1 infusion, resulting in either no or reduced insulin requirements, which in turn should reduce the incidence of hypoglycemia and avoid adverse outcomes associated with acute hyperglycemia. While not conclusively proven, there may be beneficial effects on hemodynamic outcomes. Overall, studies to date have enrolled a small number of patients and have not assessed benefit on patient important outcomes.

Several questions remain unanswered. The effective dose or range of doses needs to be determined. This dose has varied significantly in studies, although even higher doses have been well tolerated with minimal hypoglycemia and nausea. Secondly, what specific subgroup of patients will be most suitable for treatment? While patients receiving enteral feeding seem to be ideal candidates for treatment based on pathophysiology, the apparent success of GLP-1 in patients post surgery not receiving feeding suggest that it may be applicable to a broader group. Further studies are awaited regarding whether GLP-1 can be used in patients receiving gastric nutrient feeding as it decelerates gastric emptying, potentially increasing the risk of aspiration, especially given the already high incidence of delayed gastric emptying in the critically ill patient. If safe to do so, based on physiology, GLP-1 may have even greater effects on hyperglycemia if patients are fed enterally in the stomach rather than post pyloric [13]. Would it be possible to use subcutaneous injections of GLP-1 receptor agonist such as exenatide? This is now available widely for outpatient treatment of diabetes and would be easier to use especially in inpatient settings outside the intensive care unit. Also, the exact mechanism of action in patients with and without diabetes needs to be studied as evidence is conflicting regarding effects on insulin and glucagon in hospitalized patients. Finally, GLP-1 in and of itself may not cause hypoglycemia. When used in conjunction with insulin, however, effects on hypoglycemia will need to be further studied.

In summary, while initial studies of GLP-1 seem promising and leave us with a tantalizing noninsulin option for treating hyperglycemia, much research is needed before widespread application can be instituted.

Competing interests

The authors declare that they have no competing interests.

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