CRITICAL CARE

REVIEW

Incretins and the intensivist: what are they and what does an intensivist need to know about them?

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Abstract

Hyperglycaemia occurs frequently in the critically ill, even in those patients without a history of diabetes. The mechanisms underlying hyperglycaemia in this group are complex and incompletely defined. In health, the gastrointestinal tract is an important modulator of postprandial glycaemic excursions and both the rate of gastric emptying and the so-called incretin hormones, glucagon-like peptide-1 and glucose-dependent insulinotropic poly-peptide, are pivotal determinants of postprandial glycaemia. Incretin-based therapies (that is, glucagon-like peptide-1 agonists and dipeptidyl-peptidase-4 inhibitors) have recently been incorporated into standard algorithms for the management of hyperglycaemia in ambulant patients with type 2 diabetes and, inevitably, an increasing number of patients who were receiving these classes of drugs prior to their acute illness will present to ICUs. This paper sum-marises current knowledge of the incretin effect as well as the incretin-based therapies that are available for the management of type 2 diabetes, and provides suggestions for the potential relevance of these agents in the man-agement of dysglycaemia in the critically ill, particularly to normalise elevated blood glucose levels.

Hyperglycaemia and critical illness: prevalence and association with adverse outcomes

Both type 1 and type 2 diabetes mellitus (T2DM) in-crease the propensity for macrovascular and microvascu-lar disease as well as infection, all of which are likely to predispose individuals to critical illness necessitating in-tensive care admission [1]. While the worldwide preva-lence of formally diagnosed T2DM is about 3% [2], the prevalence in ICU patients is variably reported as 15 to 20% or even higher [3].

In the critically ill, hyperglycaemia also occurs fre-quently in patients without known diabetes; this group includes patients with undiagnosed type 2 diabetes and those with so-called stress hyperglycaemia. We propose that the latter should be referred to as critical illness in-duced hyperglycaemia (CIIH), given that this describes the pathogenesis more appropriately. Several hormonal mechanisms appear to be important pathophysiological mediators of hyperglycaemia during critical illness.

These mechanisms include increases in counter-regulatory hormones, such as endogenous glucagon, catechol-amines and glucocorticoids, inadequate insulin secretion for the degree of hyperglycaemia and insulin resistance [4,5]. The exogenous administration of catecholamines, dextrose, corticosteroids and nutritional support has the potential to further exacerbate the elevation in blood glucose [4,6].

CIIH is therefore characterised by hyperglycaemia (fasting blood glucose ≥7 mmol/l or random blood glu-cose ≥11.1 mmol/l) in critically ill patients, who were glucose tolerant prior to their acute illness, and are shown in the longer term not to have diabetes [1]. The true prevalence of CIIH is unknown, at least in part be-cause the vast majority of studies have failed to discrim-inate it from undiagnosed T2DM [3]. Nevertheless, CIIH is clearly common – for example, in the NICE-SUGAR study >60% of patients without known diabetes in the control arm had blood glucose concentrations >10 mmol/l requiring exogenous insulin [7].

Marked acute hyperglycaemia is associated with in-creased morbidity and mortality in the critically ill [8]. The magnitude of the elevation in blood glucose

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required to cause harm remains uncertain and is likely to differ between T2DM and CIIH. In observational studies, a robust association between increased mortality and hyperglycaemia has been reported consistently in patients with CIIH, but not in those with pre-existing T2DM [9-11]. Moreover, preliminary – albeit retrospective and observational – data suggest that the adverse impact of hyperglycaemia is attenuated or abolished by pre-existing or chronic hyperglycaemia, and that hyperglycaemia during acute illness may, in fact, be protective [12]. Accordingly, glucose concentrations that are considered safe in patients with CIIH may well be harmful in patients with type 1 or (more frequently) type 2 diabetes and chronic hyperglycaemia [12]. Furthermore, it is intuitively logical to tailor strategies for glycaemic control based on pre-existing glycaemia, rather than managing all critically ill patients as a homogeneous group. Prospective studies are urgently required in this area to clarify these important issues.

The incretin effect – the historical context

The characterisation of the incretin effect arguably began in 1902 when Bayliss and Starling, with the characterisation of secretin, speculated that the gastrointestinal tract could communicate with the pancreas via a messenger(s) in the blood [13]. Until that time, primarily as a result of Pavlov's influence, it was thought that the functions of the body were regulated exclusively by nerves. However, it was not until the early 1960s that the insulin response to enteral glucose was demonstrated to be much greater than an intravenous glucose load, despite the latter resulting in substantially higher blood glucose concentrations [14,15], suggesting that a hormone (or hormones) secreted from the gastrointestinal tract stimulates insulin secretion. When blood glucose concentrations resulting from oral and intravenous glucose load were matched, Perley and Kipnis observed that the plasma insulin response to intravenous glucose was approximately 40% of that resulting from the oral glucose load in health, quantifying the magnitude of the incretin effect for the first time [16] (Figure 1). The hormones responsible for the incretin effect were subsequently shown to be glucose-dependent insulinotropic peptide (GIP) (in 1973) and glucagon-like peptide (GLP)-1 (in 1985).

GIP is secreted predominantly from duodenal K cells in response to luminal fat and carbohydrate [17], while GLP-1 is secreted from intestinal L cells, located primarily in the distal ileum and colon, in response to luminal fat, carbohydrate, protein and bile acids [18,19]. At least in health, both GIP and GLP-1 are insulinotropic and, in the case of GLP-1, glucagonostatic in a strictly glucose-
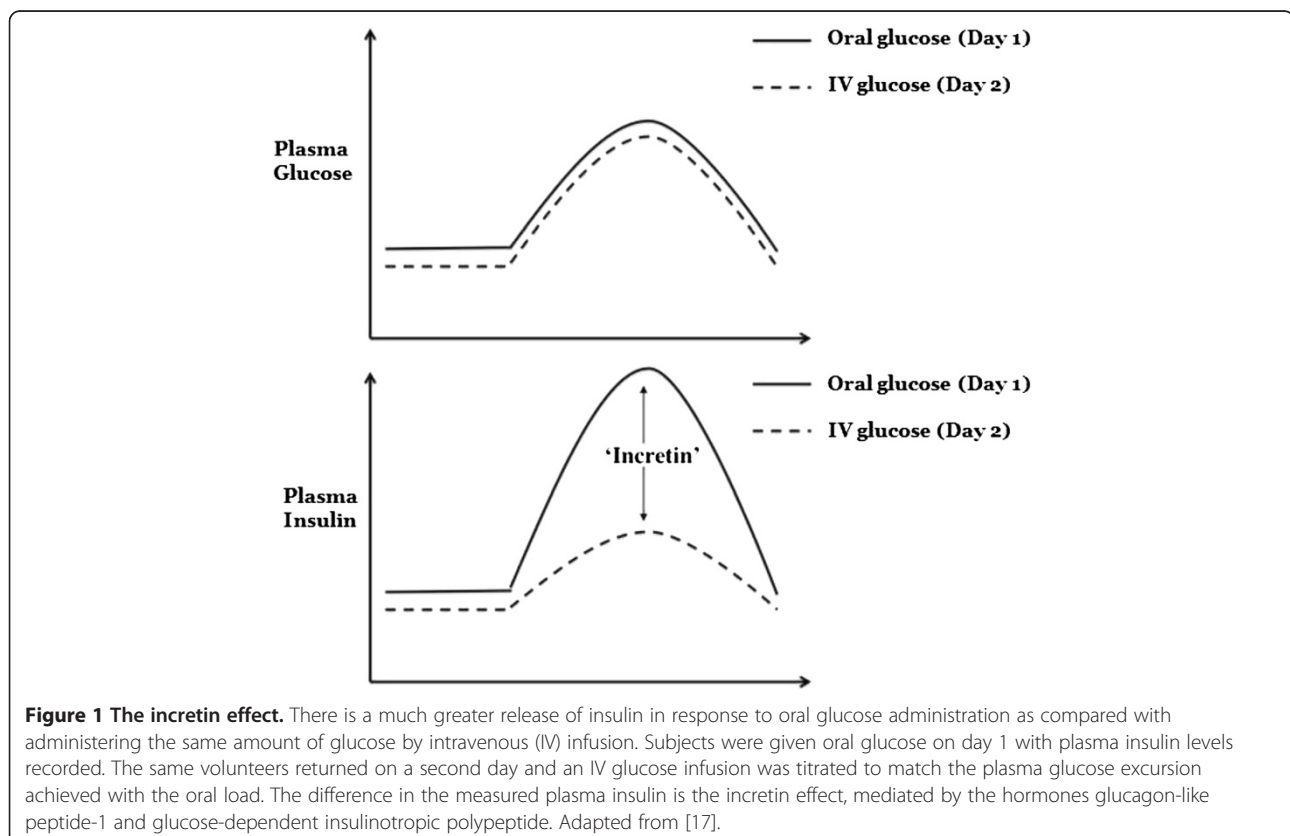

Figure 1 The incretin effect. There is a much greater release of insulin in response to oral glucose administration as compared with administering the same amount of glucose by intravenous (IV) infusion. Subjects were given oral glucose on day 1 with plasma insulin levels recorded. The same volunteers returned on a second day and an IV glucose infusion was titrated to match the plasma glucose excursion achieved with the oral load. The difference in the measured plasma insulin is the incretin effect, mediated by the hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Adapted from [17].

dependent fashion, so that below a blood glucose threshold of ~8 mmol/l even pharmacological doses of these hormones have little or no effect on fasting blood glucose [20]. In addition to its insulinotropic and glucagonostatic properties, GLP-1 is a physiological modulator to slow gastric emptying [17,21], while GIP probably has no effect on gastric emptying and is glucagonotropic during euglycaemia [22].

Attenuation of the incretin effect and pathogenesis of hyperglycaemia in type 2 diabetes

In 1986 Nauck and colleagues reported that the magnitude of the incretin effect was markedly diminished in longstanding T2DM [23], and they went on to show that the insulinotropic effect of GIP is also attenuated in this group, while that of exogenous GLP-1 is relatively preserved [24]. Whether the reduced incretin effect is a primary phenomenon or epi-phenomenon of β-cell failure is still uncertain [25], but it is apparent that the reduced insulinotropic effect of GIP is, in part, an effect of hyperglycaemia and, hence, reversible [25]. Nevertheless, these observations stimulated the development of GLP-1-based pharmacological therapy for the management of T2DM. One should recognise that a limitation of these early studies is that gastric emptying was not quantified. This is important because the rate of nutrient entry into the small intestine is a major determinant of both GLP-1 and GIP secretion [26]. Studies employing direct, intraduodenal infusion of nutrients indicate that the secretion of GIP and GLP-1 is maintained in both T2DM [26,27] and the critically ill [28].

Drug development of incretin therapies for the management of type 2 diabetes mellitus

Initial proof-of-principle studies were performed using pharmacological doses of GLP-1 administered by intravenous or subcutaneous infusion. As well as stimulating insulin [29] and inhibiting glucagon secretion, both in a glucose-dependent manner [30], GLP-1 has been shown to have several important and unique pharmacodynamic properties that enhance its therapeutic potential. GLP-1 dose-dependently slows gastric emptying, thereby attenuating postprandial glycaemic excursions [31]. Exogenous GLP-1 also inhibits appetite, resulting in reduced energy intake and sustained weight loss in obese subjects, features that are beneficial in patients with T2DM [32]. *In vitro* and animal studies have shown that GLP-1 exerts trophic effects on the pancreatic β cells, stimulating proliferation and differentiation [33], as well as reducing β-cell apoptosis [34]. Hence, GLP-1 may have the potential to preserve β-cell mass in patients with type 2 diabetes. Pharmacological administration of GLP-1 has significant extra-gastrointestinal effects with the potential cardioprotective properties of

particular relevance to the critically ill. For example: in animal models, GLP-1 attenuates ischaemia-induced myocardial damage [35]; in patients with heart failure, exogenous GLP-1 has been associated with improvements in left ventricular ejection fraction, myocardial oxygen uptake and 6-minute walking distance [36]; and when administered post-coronary artery bypass grafting, GLP-1 is associated with less use of sympathomimetic drugs and fewer arrhythmias [37]. There is evidence, hitherto derived from animal studies, that GLP-1 may possess neurotropic effects [38] which have the potential to be beneficial in the management of neurodegenerative conditions such as Alzheimer's disease [39]. The implications in the neurocritically ill remain uncertain [40,41].

Currently available incretin-based agents for use in type II diabetes

The administration of GLP-1 to ambulant patients with diabetes proved clinically impractical. Endogenous GLP-1 (and its synthetic peptide) has a plasma half-life of only 1 to 2 minutes [42] due to rapid metabolism by the ubiquitous, nonspecific enzyme dipeptidyl-peptidase 4 (DPP-4), which forms an inactive metabolite that is rapidly cleared by the kidneys [43], necessitating continuous infusion. The pharmaceutical industry has therefore focused on the development of stable DPP-4-resistant GLP-1 receptor agonists, as well as DPP-4 inhibitors that protect endogenously secreted GLP-1, GLP-2 and GIP from degradation. DPP-4 inhibitors act as incretin enhancers, increasing systemic and, perhaps of more pertinence to their effect, intestinal concentrations of endogenously secreted GLP-1, GLP-2 and GIP [44]. GLP-1 agonists are incretin mimetics, acting as agonists at the GLP-1 receptor and, in contrast to DPP-4 inhibitors, do not stimulate GIP or GLP-2 and may reduce endogenous GLP-1 concentrations [45], possibly because of its effect on gastric emptying [21].

Incretin-based therapies are frequently prescribed and their use is expected to become even more common, with recent international guidelines recommending that GLP-1 agonists and DPP-4 inhibitors be used as part of standard regimens for patients with T2DM [46].

Glucagon-like peptide-1 receptor agonists

A GLP-1 agonist candidate was fortuitously identified in the peptide exendin-4 from the salivary venom of the Gila monster (*Heloderma suspectum*). The Gila monster is a slow-moving venomous lizard native to North America that ingests food 5 to 10 times per year, and ingestion results in a substantial increase in plasma exendin-4 concentrations that may have endocrine functions related to metabolic control in the lizard [47]. Exendin-4 is a peptide with ~50% amino acid sequence homology to GLP-1 and acts as a full agonist at the

GLP-1 receptor. Exendin-4 is also resistant to metabolism by DPP-4, and is eliminated only by glomerular filtration, with a resultant plasma half-life of 30 minutes [48]. Exenatide was developed as the synthetic replica of exendin-4 and in 2005 was the first incretin-based therapy approved by the US Food and Drug Administration. There are now at least eight GLP-1 agonists undergoing clinical trials, but twice-daily exenatide, once-daily lixisenatide, once-daily liraglutide and once-weekly extended-release exenatide are the only agents to have hitherto reached the market.

GLP-1 agonists can be categorised as short-acting or long-acting compounds. All are given subcutaneously and stimulate fasting insulin secretion and reduce glucagon secretion in a glucose-dependent manner [49]. Dose-dependent nausea, vomiting and diarrhoea occur frequently, and while it is recognised as a far more prominent feature of the synthetic agonists when compared with the native peptide, it does decline with time and is attenuated by dose titration [50,51]. Short-acting and long-acting compounds do, however, differ in their effects on fasting and postprandial glucose.

Short-acting glucagon-like peptide-1 agonists

Exenatide and lixisenatide are considered short-acting GLP-1 agonists and their short half-lives result in large fluctuations in circulating plasma concentrations [49]. The dominant effect of these drugs on glycaemia is mediated by the slowing of gastric emptying, thereby markedly blunting postprandial glycaemic excursions [52]. Patients with diabetes with significant postprandial hyperglycaemia and relatively well-controlled fasting glycaemia therefore achieve the greatest benefit from these short-acting compounds. Additionally, the combination

of short-acting GLP-1 agonist and basal insulin confers complementary effects, with control of fasting hyperglycaemia by the basal insulin, control of postprandial glycaemic excursions with the GLP-1 agonists, a reduction in glycaemic variability and a low risk of hypoglycaemia [49].

Exenatide is approved in Europe as adjunctive therapy in patients with inadequately controlled T2DM who are taking oral hypoglycaemic agents or basal insulin, or both. Exenatide has also been approved for use as monotherapy in the United States. In February 2013, lixisenatide was approved in Europe as adjunctive therapy in patients with inadequately controlled T2DM, who are taking oral hypoglycaemic agents or basal insulin, or both. The pharmacological and pharmacodynamic properties of these therapies are summarised in Tables 1 and 2, respectively.

Long-acting glucagon-like peptide-1 agonists

Extended-release exenatide and liraglutide are long-acting GLP-1 receptor agonists that have continuously elevated plasma concentrations between their recommended dosing intervals. These agonists are approved in Europe and the United States to be used in the treatment of T2DM as monotherapy or as second-line therapy in combination with oral hypoglycaemic agents. They achieve higher fasting insulin levels and greater reductions in fasting glucose concentrations [49]. The continuous activation of the GLP-1 receptor is thought to induce tachyphylaxis to the deceleration of gastric emptying, such that the slowing of gastric emptying diminishes markedly with long-term use, and consequently the lowering of postprandial glycaemia is only modest [53]. Long-acting compounds therefore seem to be

Table 1 Marketed incretin-based agents

Therapy	Approval	Dose	Route	Precautions
GLP-1 receptor agonists				
Exantide (Byetta®)	EMA, US FDA	5 µg, 10 µg	SC, BD	Renal impairment[a]
Lixisenatide (Lyxumia®)	EMA	10 µg, 20 µg	SC, OD	Renal impairment[a]
Extended-release exenatide (Bydureon®)	EMA, US FDA	2 mg	SC, QW	Renal impairment[a]
Liraglutide (Victoza®)	EMA, US FDA	0.6 mg, 1.2 mg, 1.8 mg	SC, OD	MTC of MEN2
DPP-4 inhibitors				
Sitagliptin (Januvia®)[b]	EMA,US FDA	25 mg, 50 mg, 100 mg	Oral OD	Renal iAAmpairment[c]
Vildagliptin (Galvus®)[b]	EMA	50 mg	Oral BD	Renal impairment[a]
				Hepatic impairment
Alogliptin (Nesina®)[b]	US FDA	25 mg	Oral OD	Renal impairment[c]
Saxagliptin (Onglyza®)	EMA, US FDA	2.5 mg, 5 mg	Oral OD	Renal impairment[c]
Linagliptin (Trajenta®)	EMA, US FDA	5 mg	Oral OD	–

BD twice daily, *DPP-4* dipeptidyl-peptidase-4, *EMA* European Medicines Agency, *MEN2* multiple endocrine neoplasia type 2, *MTC* medullary thyroid carcinoma, *OD* once daily, *SC* subcutaneous, *QW* once weekly, *US FDA* US Food and Drug Administration. [a]Contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/minute) and end-stage renal disease. [b]Available in a fixed-dose combination with metformin. [c]Dose adjustment required in moderate (creatinine clearance ≥30 to <50 ml/minute), severe and end-stage renal disease.

Table 2 Pharmacodynamics: GLP-1 agonists versus DPP-4 inhibitors

	GLP-1 agonists	DPP-4 inhibitors
Plasma GLP-1 concentrations	Pharmacological concentrations of the GLP-1 analogue (sixfold to tenfold greater than endogenous GLP-1)	Twofold to threefold increase
Glucose-dependent insulin secretion	Yes	Yes
Glucose-dependent inhibition of glucagon secretion	Yes	Yes
HbA$_{1c}$ reduction (%)	0.8 to 1.8	0.5 to 1.1
Inhibition of gastric emptying	Short acting only	No
Postprandial glucose reduction	Yes: short acting > long acting	Yes (weaker)
Fasting plasma glucose reduction	Yes: long acting > short acting	Yes (weaker)
Effects on weight	Significant weight loss	Weight neutral
Inhibition of food intake	Yes	No
Gastrointestinal adverse effects: nausea, vomiting and diarrhoea	Common	Uncommon

DPP-4 dipeptidyl-peptidase-4, *GLP* glucagon-like peptide, *HbA$_{1c}$* glycated haemoglobin.

advantageous when clinicians wish to target fasting hyperglycaemia in patients with T2DM.

Dipeptidyl-peptidase-4 inhibitors

The DPP-4 inhibitors are orally administered agents and are approved as monotherapy or in combination with other oral hypoglycaemic agents for the management of T2DM. The predominant mechanism of DPP-4 inhibitor action is thought to be via a gut effect involving local inhibition of intestinal DPP-4 activity, stimulation of gut incretin receptors and activation of gut-to-pancreas neural pathways, rather than a systemic increase in incretin plasma concentrations [44]. DPP-4 is expressed widely throughout the body, including on T lymphocytes and macrophages, posing a theoretical risk of immune dysfunction with enzyme inhibition [54]. However, a meta-analysis reported a very minor increase in all-cause infection during sitagliptin treatment that was not evident in studies involving other DPP-4 inhibitors [55]. The reliability and significance of this association remains uncertain. The presentation, dose, contraindications and pharmacodynamics of the DPP-4 inhibitors are outlined in Tables 1 and 2.

Extra-pancreatic effects of incretin-based therapies

The cardiovascular outcomes of the incretin-based drugs are currently undergoing assessment in large, multicentre clinical trials [56]. Data from preclinical studies, short-term single-centre human studies and retrospective reviews of healthcare claims support a cardioprotective role for both GLP-1 receptor agonists and DPP-4 inhibitors [57]. The majority of clinical trials have reported reductions in body weight and blood pressure, albeit with a mean increase in heart rate of 2 to 4 beats/minute [57].

Finally, there are postmarketing reports of acute pancreatitis during use of GLP-1 agonists and DPP-4 inhibitors [58]. However, when compared with health, the risk of acute pancreatitis is more than doubled in T2DM, independent of treatment modality [59], and the incidence of pancreatitis appears to be no greater when starting these agents than in patients who are commenced on metformin or a sulfonylurea [60]. For these reasons we consider the risk of GLP-1-induced or DPP-4 inhibitor-induced pancreatitis to be negligible. There have also been concerns, principally from rodent studies, that the use of incretin-based therapies may be associated with chronic pancreatitis [61], particularly as this would intuitively also increase the risk of pancreatic cancer [62]. Hitherto, these potential risks have not been substantiated [63] and while ongoing postmarketing surveillance is important, any increase in risk is likely to be extremely small and is unlikely to be relevant to short-term use in critically ill patients.

Rationale for the use of glucagon-like peptide-1 as a novel therapy in the critically ill

Administration of intravenous insulin guided by validated algorithms is the current standard of care for hyperglycaemic critically ill patients [64]. While the optimal blood glucose for the critically ill remains contentious, concentrations >10 mmol/l should be avoided, at least for those without pre-existing diabetes and chronic hyperglycaemia [7]. Several studies have demonstrated that insulin-induced hypoglycaemia (blood glucose <2.2 mmol/l) occurs more frequently with intensive insulin therapy and that it is an independent risk factor for mortality [7,65,66]. Moreover, in the NICE-SUGAR study, moderate hypoglycaemia (≥2.3 to ≤3.9 mmol/l) and severe hypoglycaemia (<2.3 mmol/l) were both associated with insulin use and increased mortality, with the

lowest nadirs in glucose concentrations having the strongest association with death [67]. This observation may be of particular relevance in neurocritical care, particularly as there is evidence that systemic glucose concentrations even within the normal physiological range may be associated with cerebral hypoglycaemia and consequent adverse outcomes [68]. These data, accordingly, strongly suggest that treatment-induced hypoglycaemia should be avoided.

Regardless of target blood glucose, intravenous insulin therapy also carries the logistic limitations of frequent monitoring and training of nursing staff in complicated protocols. Additionally, increased glycaemic variability appears to be an independent risk factor for ICU mortality [69,70] and, although speculative, a therapy that reduces glycaemic variability may lead to improved outcomes.

By inhibiting glucagon secretion as well as increasing insulin secretion, GLP-1 or its agonists provide a plausible pharmacodynamic mechanism to counter the hyperglucagonaemia and relative insulin resistance that typifies stress hyperglycaemia. Furthermore, the cardioprotective properties hitherto demonstrated in incretin-based therapies are particularly attractive in the intensive care setting. In animal models, GLP-1 decreases ischaemia-induced myocardial damage [35]; in patients with heart failure, exogenous GLP-1 has been associated with improvements in left ventricular ejection fraction, myocardial oxygen uptake and 6-minute walking distance [36]; and when administered post-coronary artery bypass grafting, GLP-1 is associated with less use of sympathomimetic drugs and fewer arrhythmias [37].

For the reasons outlined in Table 3, a simplified therapy for the treatment of hyperglycaemia that avoided iatrogenic hypoglycaemia and limited glycaemic variability would be desirable.

Recommendations for incretin-based therapies in critically ill patients

Critical illness may markedly affect pharmacokinetics, particularly for the oral and subcutaneous routes [71].

Table 3 Potential benefits of glucagon-like peptide-1 based therapies in the critically ill

Potential benefit
Negligible risk of severe hypoglycaemia
Reduction in insulin requirement
Cardiovascular protection
Attenuated glycaemic variability
Amenable to continuous infusion without dose titration
Decreased blood glucose testing
Simplified protocol for medical and nursing staff

Furthermore, multiorgan failure with evolving hepatic and renal dysfunction and the consequent derangements in metabolism and elimination may result in unpredictable half-lives and drug clearance [71]. For these reasons, and also because of limited experience with these incretin-based agents, it is appropriate to discontinue these drugs when critically ill patients are admitted to the ICU.

In hyperglycaemic patients transitioning from intensive care to ward care, current recommended practice is to commence scheduled subcutaneous basal-bolus insulin regimens [72], although the American Diabetes Association consensus statement concedes that noninsulin agents may be appropriate in selected, stable patients who are expected to consume meals at regular intervals [72]. There have been no randomised controlled trials to compare subcutaneous basal-bolus insulin with the incretin-based agents in this patient group. However, because of the limitations inherent in basal-bolus insulin administration, in patients who were on incretin-based therapies prior to their acute illness and who are improving clinically and transitioning from the ICU to the hospital ward, recommencement of the established incretin regimen would be a reasonable therapeutic option. However, there is limited information available about the use of incretin-based agents in patients discharged from the ICU. Until such time that the strategy is formally evaluated, we recommend that intensivists using such an approach involve an endocrinologist to provide ongoing care following ICU discharge. A specialist in the field may also assist by advising dose reduction due to renal or hepatic impairment (Table 1), managing dose escalation on recommencing these agents to limit adverse effects, and being aware of potential interactions with drugs that have been commenced in the current hospital admission. Finally, because the glucose-lowering effects of GLP-1 agonists will be diminished in patients with pancreatitis, we recommend avoiding GLP-1 agonists in patients with a history of pancreatitis or surgical manipulation of the pancreas.

Experience using incretin-based therapy in the critically ill

Hitherto, the use of GLP-1 in the critically ill is limited to small studies to establish proof of principle [73]. A limitation of all of these studies has been the short duration of GLP-1 administration (<72 hours); however, in patients with T2DM, glucose lowering was maintained for up to 6 weeks during continuous subcutaneous GLP-1 infusion [74], suggesting that tachyphylaxis, at least to the glucose-lowering effect, does not occur. One should also recognise that while synthetic GLP-1 is currently prohibitively expensive, there may be a substantial reduction in cost should a market become available.

With intravenous GLP-1 infusions at doses ranging from 1.2 to 3.6 pmol/kg/minute, marked glucose lowering has been observed in patients with T2DM post-major surgery [75], post-coronary artery bypass grafting [37,76] and post-acute myocardial infarction with primary angioplasty [77]. Our group has evaluated the effects of GLP-1 infusions in heterogeneous cohorts of mechanically ventilated patients, both with T2DM and CIIH [78-80]. GLP-1 infusions at 1.2 pmol/kg/minute were shown to reduce the glycaemic response to small intestinal nutrient in mechanically ventilated patients with chronic hyperglycaemia [80] and to intragastric and small intestinal nutrient delivery in patients not known to have T2DM (Figure 2) [78,79]. At this dose, nutrient-induced hyperglycaemia was attenuated but not suppressed completely, and the effect appears to be more prominent in patients without a history of T2DM. We also reported that GLP-1 slows gastric emptying when emptying is relatively normal, but has minimal effect when emptying is already delayed, consistent with studies in ambulant type 2 diabetics [79]. The infusions were well tolerated in all patient groups and there were no reported episodes of hypoglycaemia.

Administration of intravenous exenatide is also being explored, as currently these drugs are substantially cheaper than the synthetic peptide. As outlined (Table 1), exenatide is only approved for subcutaneous administration in the ambulant type 2 patient, but there is experience with its intravenous use in trial settings [81,82]. Abuannadi and colleagues administered intravenous exenatide for 48 hours in an open-label, nonrandomised, pilot study in 40 cardiac ICU patients [83]. The effectiveness of exenatide was benchmarked to glucose concentrations previously recorded during intensive and moderate insulin therapies [83]. Mean blood glucose concentrations with intravenous exenatide were noninferior to the NICE-SUGAR-endorsed insulin protocol (that is, moderate), and glycaemic variability was reduced [83]. No episodes of severe hypoglycaemia were reported in the exenatide group, but nausea (40%) and vomiting (5%) occurred frequently [83]. Whether these agents could be used as standalone therapy or as insulin-sparing agents with the benefits of reduced hypoglycaemia and diminished glycaemic variability remains to be determined. Further studies using the commercially marketed GLP-1 agonists are warranted [84].

While studies in the critically ill have focused on GLP-1 and its agonists, the role of GIP and DPP-4 inhibitors also warrants consideration [84]. While it is known that the insulinotropic effect of GIP is markedly reduced in T2DM, this may be primarily due to hyperglycaemia rather than an inherent cellular defect [85]. In the critically ill, our group demonstrated that exogenously administered GIP with concurrent GLP-1 does not lower blood glucose concentrations, either in the fasted state or in response to small intestinal nutrient, more than GLP-1
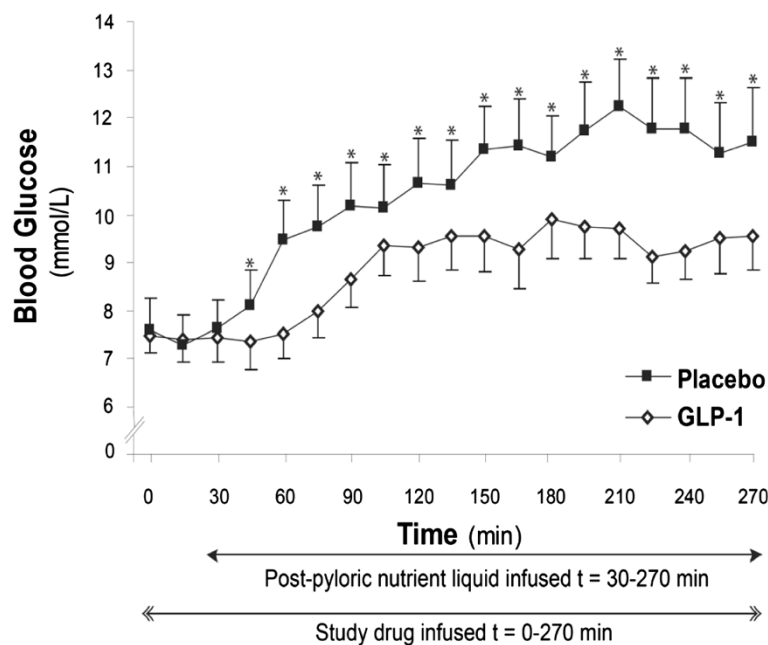
Figure 2 Glucose-lowering effect of glucagon-like peptide-1 in critical illness. In critically ill patients without known diabetes the blood glucose excursion in response to small intestinal feeding is markedly attenuated by 1.2 pmol/kg/minute glucagon-like peptide-1 (GLP-1) (area under the curve at 240 minutes: GLP-1, 2,077 ± 145 mmol/l/minute vs. placebo, 2,568 ± 208 mmol/l/minute; *P* <0.01). Data are mean ± standard error of the mean (*n* = 7). Reproduced with permission from [81].

alone [86]. However this was a small, single-centre pilot study and further research to clarify whether GIP retains its insulinotropic effect in critically ill patients, in whom blood glucose concentrations have only been transiently elevated, merits further investigation.

The DPP-4 inhibitors have not yet been investigated as a therapeutic strategy for CIIH. Delayed gastric empty-ing occurs frequently in critical illness, with absolute gastroparesis not infrequent [87], and also, at least in health, hyperglycaemia *per se* slows gastric emptying [88]. Accordingly, intragastric administration of an oral glucose-lowering drug may not be the most effective route. Nevertheless, in patients with known normal gas-tric emptying or with post-pyloric administration in pa-tients with delayed gastric emptying, the local intestinal mechanism of action supports the study of the renally safe DPP-4 inhibitor linagliptin as a potential novel oral agent for glycaemic control in the critically ill.

Conclusions

The discovery of the incretin hormones has encouraged a burgeoning pharmaceutical industry that exploits the entero-insular axis. As the prevalence of T2DM and the use of incretin-based regimens continue to rise, the intensivist is likely to encounter more patients who were taking these drugs prior to their acute illness. Presently, there is little experience with continuing these agents in acute illness and more study is urgently required.

Nevertheless, the pharmacologic strategy of adminis-tering incretin mimetics to manage acute hypergly-caemia in the critically ill, while minimising the risk of hypoglycaemia and mitigating glycaemic variability, is appealing. Future studies should focus on the identifica-tion of the patient groups most likely to benefit from the administration of incretin receptor agonists, which of the agents is most useful in the critically ill, and at what dose, the relevance of the route of feeding with concur-rent incretin therapy and, finally, whether these agents should be used in combination with insulin or as single-agent therapy to provide a safer, more effective and sim-pler method of achieving glycaemic control.

Abbreviations
CIIH: Critical illness induced hyperglycaemia; DPP-4: Dipeptidyl-peptidase-4; GIP: Glucose-dependent insulinotropic polypeptide; GLP: Glucagon-like peptide; T2DM: Type 2 diabetes mellitus.

Competing interests
MH has participated in advisory boards and/or symposia for Novo/Nordisk, Sanofi-aventis, Novartis, Eli-Lily, Boehringer Ingelheim, AstraZeneca, Satlogen and Meyer Nutraceuticals. The remaining authors declare that they have no competing interests.

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