CME New Therapeutic Agents for Diabetes Mellitus: Implications for Anesthetic Management

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Multiple hormones and transmitter systems contribute to glucose homeostasis and the control of metabolism. Recently, the gastrointestinal peptide hormones glucagon-like peptide 1 and amylin have been shown to significantly contribute to this complex physiology. These advances provide the foundation for new treatments for diabetes mellitus. Therapies based on glucagon-like peptide 1 and amylin have now been introduced into clinical practice. Rimonabant, the selective endocannabinoid receptor antagonist, had been used in European countries for the treatment of obesity; it has recently been withdrawn for this indication. This drug exhibited therapeutic benefits for metabolic variables and for type 2 diabetes mellitus. Anesthesia providers caring for patients with diabetes mellitus will need to understand the implications of these new therapies in perioperative settings, particularly with respect to side effects and interactions.

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Diabetes mellitus (DM) is a condition with an absolute (Type 1) or relative (Type 2) deficiency of insulin. Significant end-organ consequences of both types of diabetes include renal, neurological, cardiovascular, and peripheral vascular pathology that may have an impact on the perioperative course. Multiple hormones and neural systems control glucose homeostasis. The principle regulator of plasma glucose levels is insulin, a polypeptide secreted by pancreatic β cells. The plasma glucose decreasing action of insulin has long been recognized and its effect is counter-regulated by epinephrine, growth hormone, cortisol and glucagon, a polypeptide secreted by pancreatic α cells. Conventional therapies for DM have recently been reviewed.[1–4] Table 1 presents a summary of the major classes of medications used in the treatment of DM.

Contemporary studies revealed that two new families of gastrointestinal (GI) hormones, represented by the incretins and amylin, have significant effects on glucose homeostasis. In addition, antagonists of the endocannabinoid system acting at the CB1 receptor, represented by rimonabant, were found to exert multiple effects on food intake and metabolic variables, including glucose homeostasis. These advances provide new opportunities for therapeutic approaches to patients with DM. Anesthesia providers will increasingly encounter patients treated with novel drugs based on the enhanced understanding of glucose homeostasis and the physiological control of metabolism. We aim to provide anesthesia clinicians with an introduction to the rapidly evolving pharmacology of medical treatment for DM.

BIOLOGY OF INCRETINS

Identification of the members of the incretin family of endogenous gut hormones was based on the observation that the insulin response to oral glucose loads is more vigorous than from IV glucose loads producing the same blood glucose levels. In human studies, when subjects achieve identical plasma glucose increases, oral glucose administration resulted in more insulin secretion than IV glucose administration (Fig. 1).[5–9] This indicated that previously unidentified factors produced by the GI system influence blood glucose levels in combination with the known hormones, insulin and glucagon. The consequence of these gut factors is called the "incretin" effect.

The incretin effect is mediated via GI hormones that stimulate insulin secretion in response to glucose increase from an enteral carbohydrate load. GIP (glucose-dependent insulinotropic polypeptide) and glucagon-like peptide 1 (GLP-1, Fig. 2) are the first two incretin hormones identified. Because much of GIP's insulinotropic effect is lost in diabetic patients due to resistance to its actions, its potential utility in diabetic therapy is low[7,10] and therefore will not be discussed further. Unlike GIP, GLP-1's insulinotropic

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Table 1. Classes of Agents Regulating Glucose Levels

Class	Route	Mechanism of action	Side effects	Clinical agents
Insulin	SQ, IV	↑ Glucose uptake	Hypoglycemia	Many preparations
GLP-1	SQ	↑ Insulin secretion (if hyperglycemia) ↓ Glucagon secretion ↓ Appetite ↓ Gastric emptying	Nausea	Exenatide
Amylin	SQ	↓ Postprandial glucagon secretion ↑ Satiety ↓ Gastric emptying	Hypoglycemia (with insulin) Nausea	Pramlintide
DPP-IV inhibitor	Oral	↓ GLP-1 degradation	Infection	Sitagliptin
Cannabinoid receptor antagonist	Oral	Weight loss Multiple other effects	↓ Glucose Depression ↓ Appetite	Rimonabant
Sulfonylurea	Oral	↑ Insulin secretion via binding to specific receptor on β cells	Hypoglycemia Hyponatremia Drug-drug interactions	Chlorpropamide Glimepiride Glipizide Glyburide Tolazamide Tolbutamide
Meglitinide	Oral	↑ Insulin secretion by binding to ATP dependent K^+ channels on β cells	Hypoglycemia	Repaglinide Nateglinide
Thiazolidinedione	Oral	Insulin sensitizer by binding to PPAR γ receptor	Edema, anemia, obesity, CHF, hepatotoxicity	Rosiglitazone Pioglitazone
Biguanide	Oral	↓ Hepatic glucose output Insulin sensitizer	Lactic acidosis Diarrhea	Metformin
Alpha-glucosidase inhibitor	Oral	↓ GI glucose absorption by inhibiting enzyme that metabolizes complex carbohydrates	Malabsorption Flatulence Diarrhea	Acarbose Miglitol

Incretin-mimetics (GLP-1, DPP-IV inhibitors) and insulin sensitizers (thiazolidinediones, biguanides) in single agent therapy do not predispose to hypoglycemia even in the fasting state.
CHF = congestive heart failure; SQ = subcutaneous; DPP-IV = dipeptidyl pepidase IV; GLP-1 = glucagon-like peptide 1.

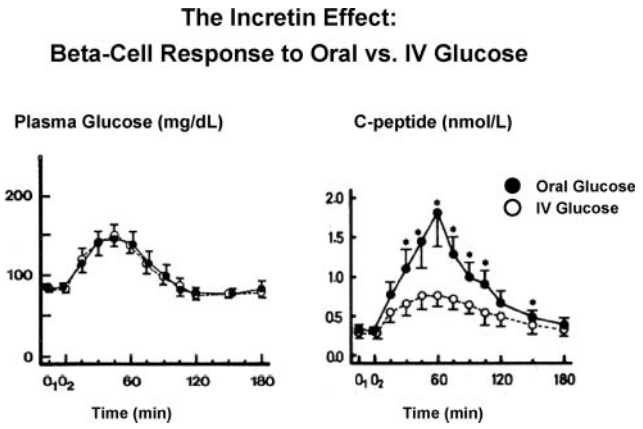

Figure 1. Insulin secretion after IV or oral glucose load. Subjects received oral glucose (50 g glucose/400 mL) or an IV infusion of glucose to produce the same blood glucose levels. As measured by plasma levels of C-peptide (a fragment of the insulin prohormone), oral glucose loading (solid circles) resulted in a greater secretion of insulin compared with IV glucose loading (open circles) designed to achieve identical plasma glucose concentrations. The difference between insulin secretion profiles after oral versus IV loading is defined as the incretin effect. Left, plasma glucose after oral or isoglycemic IV loading of glucose. Right, C-peptide levels in response to oral or IV glucose loading. Modified from Ref 5, with publisher's permission from the Endocrine Society.

action persists in patients with DM.[10] This makes it a potential target for diabetic therapy. Initial studies identified enteroendocrine L cells located in the distal ileum and large intestine as the source of GLP-1. One study also found enteroendocrine L cells located more proximally in the duodenum and jejunum.[11] The fasting blood GLP-1 level is approximately 5–10 pmol/L. Within minutes of food intake, the level increases to 15–50 pmol/L.[11] The rapid increase in blood levels of GLP-1 suggests that the secretion of GLP-1 is not simply due to detection of nutrients by the L cells in the digestive tract; a faster endocrine/neural signaling system must also be involved.[11]

The peptide hormone GLP-1 reduces appetite, slows gastric emptying, reduces glucagon levels, enhances glucose- stimulated insulin secretion, and increases insulin biosynthesis (Table 1).[9,11,12] In animal models, GLP-1 has trophic actions to increase the numbers of pancreatic β cells.[13] GLP-1 works through a G protein coupled signal transduction system, and its receptors are found in pancreatic α and β cells, the central nervous system, and the GI tract. Through its receptors on β cells, GLP-1 enhances insulin exocytosis, but only in a glucose-dependent manner.[7] GLP-1 induces gene transcription in pancreatic β cells to promote insulin biosynthesis. *In vitro* studies demonstrate that GLP-1 influences β cell survival by promoting

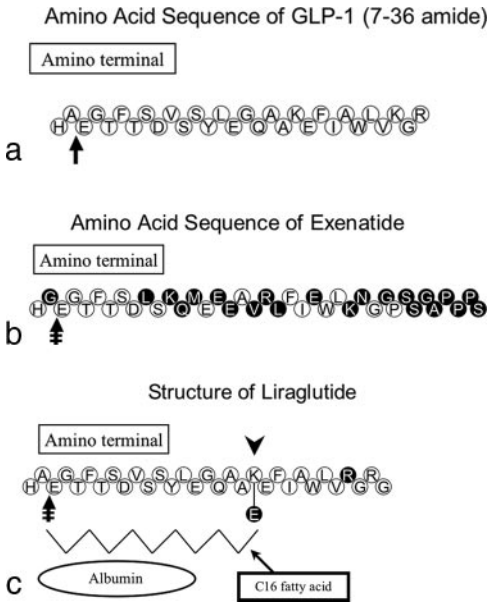

Figure 2. Structure of the peptide glucagon-like peptide 1 (GLP-1) and analogs. a, Amino acid sequence of the mammalian peptide GLP-1. Arrow at the amino terminus indicates site of cleavage by the ubiquitous peptidase, dipeptidyl peptidase IV (DPP-IV). DPP-IV preferentially cleaves peptides with proline (P) or alanine (A) in the second amino terminal position. b, Amino acid sequence of the naturally occurring peptide exenatide. This peptide is resistant to degradation by DPP-IV because of the substitution of glycine (G) at the second amino terminal position (hatched arrow). It exhibits a biological profile similar to the endogenous mammalian peptide, GLP-1. c, Structure of the synthetic GLP-1 analog liraglutide. This peptide is covalently modified with a C16 fatty acid chain via the addition of a glutamic acid (E) to the native lysine (K) as indicated by the arrowhead. The modified peptide binds noncovalently to albumin. This hinders degradation by DPP-IV. Incretin biological activity is preserved.

proliferation and resistance to apoptosis.[14] Through its receptors on α cells, GLP-1 inhibits glucagon secretion in a glucose-dependent manner and consequently reduces hepatic glucose production. The counter regulatory release of glucagon in response to hypoglycemia remains active.[15] Through actions on the central nervous system, GLP-1 decreases appetite and food intake with a resulting contribution to weight loss.[12,15] GLP-1 also slows gastric emptying, thereby blunting the postprandial increase in blood glucose levels.[6]

A feature of the biology of GLP-1 is its rapid degradation by the peptidase dipeptidyl peptidase IV (DPP-IV) (Fig. 2a).[9,16] DPP-IV cleaves peptides at their amino terminal where the penultimate amino acid residue is proline or alanine.[16] The presence of DPP-IV in the capillary bed of the gut mucosa facilitates rapid inactivation of GLP-1.[17] DPP-IV is a ubiquitous, membrane-spanning, cell surface aminopeptidase. Its extracellular domain can be cleaved and circulate in the plasma, retaining full enzymatic strength. DPP-IV is also found in liver, lung, kidney, the intestinal brush border, lymphocytes and endocrine cells. In addition to GLP-1, DPP-IV has numerous substrates, including vasoactive intestinal polypeptide, gastrin-releasing peptide, neuropeptide Y and growth hormone-releasing hormone.[18,19] DPP-IV also has a role in the immune system. It is found on lymphocytes as CD26, which has been implicated in cellular uptake of the Human Immunodeficiency Virus.[20] Other biological effects of DPP-IV include actions on T cell activation, chemotaxis and possibly tumor transformation and invasion.[21]

Compared with healthy individuals, patients with DM exhibit a blunted increase in blood GLP-1 levels after food intake.[22] Consequently, experimental treatment for DM has evaluated treatment with the native GLP-1 peptide. However, since DPP-IV rapidly degrades GLP-1, only a constant IV infusion of the peptide is effective in sustaining therapeutic plasma levels. Two pharmacological strategies are now clinically used to counter the effects of the DPP-IV peptidase (Table 2).[7,8] One strategy uses injection of a GLP-1 analog resistant to DPP-IV. A second pharmacological strategy targeting DPP-IV uses an inhibitor of this peptidase in order to increase levels of endogenous GLP-1.

Specific Agents

The naturally occurring peptide homolog of GLP-1, exendin-4, resists degradation by DPP-IV. The synthetic form is known as exenatide; its commercial name is Byetta®. Exendin-4/exenatide is originally derived from salivary secretions of the lizard *Heloderma suspectum* (the Gila monster) and shares roughly 50% of its amino acid sequence with mammalian

Table 2. Pharmacologic Agents Acting via the Incretin and Amylin Pathways

Agent	Mechanism of action	Major side effects	Time to onset (h)	Duration of action (h)
Exenatide (Byetta®)	Incretin-mimetic, increases insulin secretion only with hyperglycemia	Risk of hypoglycemia when given with a sulfonylurea; delay in gastric emptying, nausea, anorexia	<0.25	6–12
Sitagliptin (Januvia®)	Inhibitor of DPP-IV	Upper respiratory infections, headache	Peak at 1–4 h	Half life approximately 12
Pramlintide (Symlin®)	Amylin analog, suppresses postprandial glucagon secretion	Hypoglycemia when given with insulin, delay in gastric emptying, nausea	<0.25	2–4

DPP-IV = dipeptidyl pepidase IV.

GLP-1.[23] However, a substitution of glycine for alanine in its amino terminal protects exenatide from degradation by DPP-IV (Fig. 2b).[11] Exenatide has a circulating half-life variously reported between 60 and 90 min to 2.5 h, with plasma concentrations lasting 4 to 6 h or more after a single subcutaneous dose. Elimination is primarily through the renal system, although patients with mild to moderate renal impairment do not exhibit significantly altered clearance.[23]

Exenatide is currently approved for the treatment of type 2 DM patients receiving concurrent metformin or sulfonylurea therapy.[23] It has no role in therapy of patients with DM type 1. Exenatide is given as a subcutaneous injection of 5 to 10 μg twice daily. Clinical trials show a significant reduction in hemoglobin A1c levels over 30 wk (absolute reduction of approximately 0.6%–0.9% from baseline hemoglobin A1c of 8.2%–8.7%) and a modest amount of weight loss (2 kg over 30 wk).[24]

The most common adverse events were GI symptoms, including nausea and, rarely, vomiting or diarrhea.[25] Patients receiving both exenatide and a sulfonylurea exhibit an increased risk for mild to moderate hypoglycemic events. However, the risk was not increased in patients receiving concurrent treatment with exenatide and metformin.[25] Approximately, 40% to 50% of patients receiving exenatide develop low titers of a weak affinity antibody. However, the antibody formation has not been associated with decreased effectiveness of exenatide or other adverse reactions.[11]

A long-acting exenatide preparation is currently under development, a polylactide-glycolide microsphere suspension containing 3% exenatide peptide. In diabetic rats, this preparation produced dose-dependent control of serum glucose for up to 28 days after a single injection.[11]

Liraglutide is another GLP-1 analog. With amino acid substitutions at positions 34 and 26, and a covalently linked C16 fatty-acid group, liraglutide forms noncovalent bonds with albumin, which confers resistance to DPP-IV-mediated degradation (Fig. 2c).[11] It is not yet released in the United States for clinical use. Like exenatide, liraglutide is given as a subcutaneous injection. It has a half-life of 10–14 h and consequently can be given as a once-daily injection. Clinical trials with liraglutide demonstrated significant reductions in postprandial glucose levels.[11] Reduced hemoglobin A1c levels (absolute reduction of approximately 0.8% from baseline hemoglobin A1c) suggest improved long-term glucose control.[25] Liraglutide also prevents weight gain or induces modest weight loss.[11] The most common adverse event is nausea, which is generally mild and decreases over time.

Sitagliptin is a DPP-IV inhibitor, now commercially available in the United States. The trade name is Januvia®. Other DPP-IV inhibitors, including vildagliptin, are in clinical trials and may soon be approved for routine use.[18] Sitagliptin enhances insulin secretion and decreases glucagon secretion

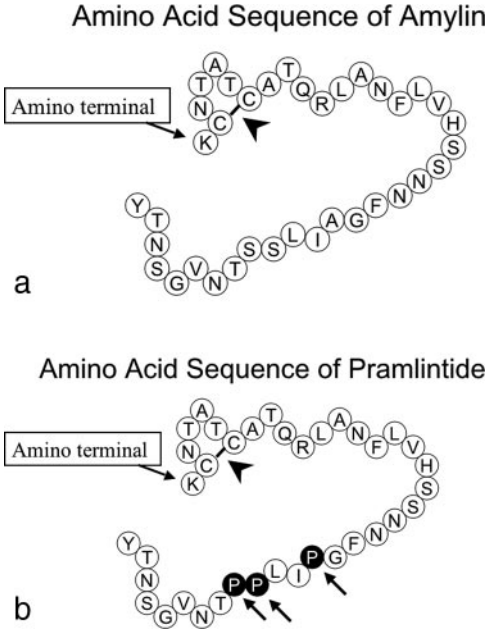

Figure 3. Structure of amylin and the synthetic analog pramlintide. a, Amino acid sequence of the naturally occurring peptide hormone. Arrowhead indicates the disulfide bridge between two cysteines. b, Structure of the synthetic amylin analog pramlintide. Substitution with proline at positions 25, 28, and 29 of the native peptide (arrows) confers solubility without disrupting biological activity. Arrowhead indicates the disulfide bridge between two cysteines.

in a glucose-dependent matter. However, unlike exenatide and liraglutide, sitagliptin does not affect gastric emptying.[26] It has a half-life of 12 h and is taken orally as a once or twice daily medication. Clinical trials have shown a significant reduction in hemoglobin A1c levels associated with sitagliptin therapy (absolute reduction of 0.8% from baseline hemoglobin A1c of 5.8%–10.4% over 3 mo).[26] Unlike therapy with exenatide, there was no significant weight change associated with sitagliptin. In early clinical trials, sitagliptin seemed to be well tolerated, without significant GI symptoms or hypoglycemic events.[26] However, given widespread expression of DPP-IV in many cell types, and multiple potential substrates for this peptidase,[8] additional clinical studies are needed to assess the long-term safety of DPP-IV inhibitors.[18]

BIOLOGY OF AMYLIN

Amylin, another GI hormone, has been identified as a potential therapeutic target in DM (Fig. 3a).[8,27] Pancreatic β cells, the same cells that manufacture and secrete insulin, produce the amylin peptide hormone. Consequently, patients lacking functional pancreatic β cells (individuals with type 1 DM or advanced type 2 DM) are deficient in both insulin and amylin.[27] Similar to GLP-1, food intake stimulates amylin secretion. Its 24-h profile resembles that of insulin, with low fasting blood levels and a robust increase in response to meals. The glucose-decreasing effect of amylin seems

to be independent of, and additive to, the effects of insulin.[28]

Like GLP-1, the actions of amylin include suppression of glucagon secretion in a glucose-dependent manner and delayed gastric emptying (Table 1); however, the mechanism(s) of action remain incompletely defined. Amylin is also a satiety agent, with receptors in the area postrema of the hindbrain.[28] By suppressing glucagon secretion and delaying gastric emptying, amylin slows the inflow of glucose into the circulation. At the same time, insulin stimulates cellular uptake of glucose to reduce postprandial blood glucose levels. Effort has been made to treat patients with diabetes using the native amylin peptide. However, endogenous amylin aggregates and forms insoluble masses of amyloid. Consequently, synthetic modifications are necessary to produce a soluble amylin analog suitable for clinical use.

Specific Agent

Pramlintide is a synthetic amylin analog with proline substitutions at amino acid positions 25, 28, and 29 (Fig. 3b).[27] These structural changes improve solubility. Pramlintide is used as an adjunct to insulin for both type 1 and type 2 DM patients. It is given as a subcutaneous injection two or three times daily. Pramlintide has an onset of approximately 20 min and duration of action of about 2 to 4 h. Clinical trials demonstrated significant improvement of postprandial glucose levels and hemoglobin A1c levels (absolute reduction of 0.67% at 13 wk and 0.39% at 52 wk) associated with pramlintide treatment.[24] Pramlintide seems to decrease postprandial triglyceride excursions.[29] The most common adverse reaction associated with pramlintide therapy is nausea, which improves over the course of treatment. By itself, pramlintide has not been shown to cause an increased risk of hypoglycemia; however, any concurrent insulin dose needs to be adjusted to prevent hypoglycemia.[27]

THE ENDOCANNABINOID SYSTEM

A comprehensive overview of the astonishingly complex endocannabinoid signaling system is beyond the scope of this article. Detailed reviews are available.[30] Briefly, the identification of specific binding sites for plant products led to the identification of two G protein-coupled receptors, labeled CB1 and CB2. The CB1 receptor is widespread throughout the brain and peripheral tissues, whereas the CB2 receptor has a more restricted distribution. These receptors seem to use several different signal transduction pathways, depending on how the receptor is activated and the tissue where it is expressed. The diverse distribution of the CB1 receptor, in particular, explains the extensive array of biological activities associated with its activation or blockade which include effects on appetite and ingestive behavior, addictive behaviors, sleep/awake cycles, peripheral energy metabolism, pain and inflammation.

The isolation of specific receptors for exogenous agonists suggested the existence of endogenous ligands for the two cannabinoid receptors. Several candidate ligands have been identified. These include anandamide, derived by enzymatic hydrolysis from the membrane lipid precursor N-arachidonoyl phosphatidylethanolamide, and 2-arachidonoylglycerol derived from diacylglycerol. Of compelling interest for the administration of anesthesia, there is evidence that propofol acts, at least in part, via activation of CB1 receptors.[31] This effect may be mediated by the inhibition of anandamide breakdown.[32] Schelling et al.,[33] however, provided evidence that the inhaled general anesthetic sevoflurane has different effects on anandamide levels than does propofol, suggesting agent-specific interactions with the endocannabinoid system.

Specific Drug

Rimonabant was available until recently in many countries (trade name: Acomplia), primarily as a treatment for obesity, with an added benefit of improving glucose homeostasis beyond what might be expected from weight loss alone.[34,35] Clinical trials with rimonabant (such as the Rimonabant in Obesity trial) demonstrated sustained weight loss and a reduction in waist circumference. In addition, metabolic profiles improved for triglyceride levels, lipoprotein cholesterol levels, and insulin resistance. Consequently, considerable interest developed in this drug for the management of metabolic syndrome.[34,36] This drug has multiple pharmacologic effects[37] and a long terminal elimination half-life in animals (approximately 7 h). A prominent finding is that treatment with rimonabant is associated with neuropsychiatric side effects.[38] Out of concern for an enhanced risk of depression and suicide,[39] rimonabant was not approved in the United States[40] and it has recently been withdrawn in Europe for the original indication of obesity.

ANESTHETIC CONSIDERATIONS

A literature search via the National Library of Medicine tool PubMed does not produce published examples of adverse effects, drug-drug interactions or clinical conundrums attributable to exenatide, pramlintide, a DPP IV inhibitor, or rimonabant in patients undergoing anesthesia or surgery. These drugs have only recently appeared in clinical practice, and only a subset of all treated patients may have required an anesthetic since the drugs were approved and released. Consequently, the number of clinical situations in which a potential adverse effect emerges may be too few for the manifestation of an uncommon reaction.

Alternatively, adverse effects may have occurred, but went undetected in complex clinical scenarios in which patients suffering from multiple co-morbid conditions received several medications concurrently.

Moreover, untoward effects in anesthetized or surgical patients attributable to one of these newly released drugs simply may not have been reported. As clinical experience with these new drugs increases, it is possible that recognizable patterns will develop. Therefore, at this time it is only possible to suggest potential anesthesia concerns based on the known physiology and pharmacology of the novel therapies.

Nausea is the most common adverse reaction associated with medications active along the incretin and amylin pathways. Clinical trials have shown nausea occurring in as many as 57% of patients treated with exenatide.[41] The incidence of vomiting is less frequent. However, vomiting still occurs in approximately 17% of the patients receiving exenatide.[41] Nausea is generally mild to moderate, and most prevalent in the first 8 wk of treatment. The frequency and intensity of nausea generally declines thereafter. The risk of nausea is dose-dependent and can be decreased by gradual dose titration. However, adverse GI effects associated with exenatide are still the most common causes for patients to withdraw from clinical trials.[41]

Clinical studies with DPP-IV inhibitors, such as sitagliptin, have reported no increased GI adverse reactions. They are overall well tolerated with low absolute rates of adverse effects.[26] This lack of GI adverse reactions may be secondary to the fact that DPP-IV inhibitors only moderately increase the levels of endogenous incretin hormones. In contrast, administration of incretin analogs, such as exenatide, increases incretin hormone activity to a much greater extent. Similar reasoning explains the finding that, while incretin analogs cause significant weight loss in patients, DPP-IV inhibitors usually do not produce significant weight changes.

Nausea is the most common adverse effect of pramlintide, the amylin analog. Nausea occurs more frequently in the type 1 DM patient than in the type 2 DM patient.[27] It is usually mild to moderate in intensity, occurring most frequently in the early stage of treatment, and commonly attenuates over time. The incidence of nausea is approximately 47% in type 1 diabetics and 27% in type 2 diabetics.[42] The risk of nausea depends on the dose of pramlintide and can be decreased by gradual dose titration.

Prominent antinausea effects of cannabinoids may be mediated, at least in part, by CB1 receptors. This has led to occasional use of cannabinoids for patients receiving cancer chemotherapy.[30] In a meta-analysis of studies on the use of rimonabant in smoking cessation, nausea was one of the adverse effects emerging from the pooled data from the early trials.[43]

Although there are no published reports of unusual postoperative nausea and vomiting (PONV) attributed to rimonabant or to drugs active along the incretin and amylin pathways, it seems reasonable to expect that patients treated with these medications may experience more frequent, or more severe, PONV than the average patient. Consequently, for elective surgery requiring anesthesia, at this time it seems logical to withhold these medications in the immediate perioperative period to reduce the likelihood or intensity of PONV. In situations of urgent or emergency surgery, without an opportunity to halt the administration of these novel drugs, it is possible that patients will exhibit exaggerated or refractory postoperative nausea. Future clinical studies may eventually provide evidence-based recommendations.

Delaying gastric emptying is one of the mechanisms by which incretin peptides and amylin decrease postprandial glucose levels.[6] By impeding gastric emptying, glucose inflow into the circulation slows. Consequently, the incretins and amylin allow insulin more time to stimulate glucose uptake and regulate serum glucose levels. Both exenatide and pramlintide cause delayed gastric emptying. DPP-IV inhibitors, such as sitagliptin, however, have little or no effect on gastric emptying,[26] probably attributable to the modest increases in GLP-1 levels caused by this class of drugs. Gastroparesis is a feature of advanced diabetes, and medications that slow gastric emptying may exacerbate this problem.[44] Although no published reports document an increased risk of aspiration associated with the new diabetes therapies, patients receiving these medications are theoretically at a greater risk for this complication during the perioperative period, especially those patients with peripheral neuropathy and gastroparesis as manifestations of their diabetes. In urgent or emergent situations where there has been no opportunity to withhold the medications, clinicians may find unexpectedly large volumes of gastric contents removed by gastric suction. The administration of drugs promoting gut motility, such as metoclopramide, might factor more prominently in overall management of the patient unless there are specific contraindications.

Hypoglycemia is a potential adverse effect of medications active along the incretin and amylin pathways, particularly if used in conjunction with an insulin preparation or a sulfonylurea. Because incretin analogs only promote insulin secretion in a "glucose-dependent" manner and because the counter-regulatory release of glucagon secondary to hypoglycemia is preserved with incretins, the risk of hypoglycemia should be low. Clinical trials show that severe hypoglycemia requiring medical intervention is rare with incretin analogs, such as exenatide. In 1 trial, only 5 of 2781 patients treated with exenatide had hypoglycemia requiring medical assistance.[45] All five patients also received an insulin secretagogue, such as a sulfonylurea. No patients receiving both exenatide and an insulin sensitizer, such as metformin, developed hypoglycemia requiring medical assistance.

When clinical trials are combined and reviewed under meta-analysis, the overall incidence of hypoglycemia associated with exenatide is approximately

16%.[41] Hypoglycemia occurs especially when exenatide is co-administrated with a sulfonylurea. This risk is comparable with the risk of hypoglycemia for patients receiving insulin for treatment of diabetes. The likelihood of hypoglycemia is greatest during the initial treatment period and declines over time. When compared with incretin analogs, DPP-IV inhibitors carry less risk of hypoglycemia. In meta-analysis, only approximately 1.6% of patients had episodes of mild to moderate hypoglycemia, which was not statistically different from the control group.[41]

Clinical trials with the amylin analog pramlintide showed no increase in the overall event rates for severe hypoglycemia.[46] However, in patients also receiving insulin for their diabetes, the rate of hypoglycemia increased during the initial 4 wk of therapy with pramlintide.[46] The enhanced risk of hypoglycemia was transient and diminished with appropriate blood glucose monitoring and adjustments of insulin dose.

The half-lives and clinical effects of sitagliptin, exenatide, and pramlintide are relatively short. Furthermore, no clinical reports suggest that medications active along the incretin or amylin pathways cause hypoglycemia in the perioperative period. However, in the absence of definitive evidence, the theoretical risk of hypoglycemia is another reason to withhold these medications in advance of elective surgery. This would be a particularly pertinent consideration for patients receiving both a sulfonylurea or an insulin preparation and exenatide. Suppression of glucagon release by exenatide would be a mechanism contributing to hypoglycemia. Should longer-acting GLP-1 analogs, such as liraglutide, enter into clinical use, the glucose-decreasing effects might extend into the surgical or anesthesia interval. Anesthesia providers routinely monitor the blood glucose levels of their patients. Perhaps, however, particular vigilance for the possibility of hypoglycemia is warranted, especially in urgent/emergent surgical situations in which there is no opportunity to withhold the medications. In theory, patients treated with long-acting insulin preparations or sulfonylureas along with exenatide would be most vulnerable. Clinicians might consider more frequent monitoring in urgent or emergent situations.

Hypoglycemia does not seem to be a likely consequence of rimonabant therapy.[35]

OTHER EFFECTS

DPP-IV is a ubiquitous aminopepetidase with multiple natural substrates and it plays a role in the immune system. Consequently, it seems plausible that inhibiting DPP-IV can potentially cause adverse reactions. Clinical trials have shown that DPP-IV inhibitors were very well tolerated with low rates of adverse effects. In meta-analysis, there is a small increased risk of nasopharyngitis and urinary tract infection associated with DPP-IV inhibitors.[41] Clinical experience in anesthetized patients receiving DPP-IV inhibitors is limited. Because multiple peptides are potential substrates for this enzyme,[18] clinicians should be alert for unusual reactions, especially in urgent procedures in which the drug may not have been withheld.

The endocannabinoid system is involved in many complex behaviors and physiologic responses, including pain and sleep/awake cycles. In preclinical studies, as cited above, there appear to be interactions between the endocannabinoid system and anesthetics. Given the "pleiotropic" effects of rimonabant,[37] the exact consequences of clinical interactions between drugs acting on cannabinoid receptors in the brain and periphery with sedatives, narcotics, and inhaled or injected general anesthetics remain to be determined.

SUMMARY AND RECOMMENDATIONS

Food ingestion increases secretion of insulin, amylin, and the incretin peptides. Insulin and amylin regulate postprandial hyperglycemia, while amylin also suppresses glucagon secretion and slows food intake and gastric emptying. GLP-1 amplifies glucose-stimulated insulin release, in addition to suppressing glucagon secretion, food intake, and gastric emptying. The new treatment options for DM acting along the incretin pathway and the amylin analog offer some potential advantages for chronic treatment of DM by targeting these physiologic mechanisms. However, the biological activities of these drugs may present challenges in the perioperative period. This is especially true in the urgent or emergent clinical circumstances in which there are no opportunities to withhold these medications.

As clinical experience accumulates with novel drugs in anesthetized patients, it may become possible to develop more definitive warnings and recommendations. However, until this information becomes available, we suggest withholding GLP-1 analogs, DPP-IV inhibitors, and pramlintide on the day of surgery. Patients can probably continue to take these drugs the day before surgery without an enhanced risk of hypoglycemia while fasting. With these drugs, there are potentially enhanced risks of nausea, aspiration of gastric contents, and hypoglycemia.

As the newer treatments for DM become increasingly prevalent in clinical practice, anesthesia providers should maintain particular vigilance for unusual or exaggerated effects and responses during the perioperative period.

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