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Posted Date: 5 November 2024

doi: 10.20944/preprints202411.0253.v1

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 doi:10.20944/preprints202411.0253.v1

Review

Modern Hypoglycemic Agents and Their Perioperative Implications

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Abstract: There are far more options to treat diabetes now, than about 15-20 years ago. Among the newer agents, glucagon-like peptide 1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium-glucose cotransporter 2 inhibitors (SGLT-2i), are in common use. While their benefits extend far beyond the management of hyperglycemia, some pose concerns, and challenges to the anesthesia providers. Retained gastric contents due to slow gastric emptying is a significant drawback of GLP-1RA. It benefits the patient in losing weight; however, increases the risk of aspiration and can surprise an unsuspecting anesthesia provider. National associations have issued statements in an effort the mitigate the risk. Recommendations range from withholding of GLP-1RA for a predefined period of time, gastric ultrasound to evaluate the gastric contents and modification of anesthesia management especially with regards to the airway and cancellation of a scheduled (elective) surgery/procedure. SGLT-2i are known to increase the risk of euglycemic ketoacidosis. Duration of preprocedural withholding of SGLT-2i varies with the drug. Use of both GLP-1RA and SGLT-2i extends beyond the treatment of diabetes. While SGLT-2i are being extensively used to treat obesity, they are also used in the management of heart failure. A new insulin formulation of basal insulin that can be administered once weekly to achieve similar blood sugar control as once daily formulation has become available in some countries. Labelled as icodec, this is as yet not approved by the FDA because of severe hypoglycemia concerns. Imeglimin is a variant of metformin with unique mechanisms of action. It is approved for clinical use for type 2 diabetes in Japan and India. Another, as yet investigational product is IcoSema, a once-weekly combination of insulin icodec plus semaglutide. A discussion of all aspects of these drugs is warranted.

Keywords GLP-1RA; SGLT-2i; Gliptins; Icodec; IcoSema; Imeglimin; dipeptidyl peptidase-4 inhibitors; DPP-4i

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The last 2 decades have presented remarkable flexibility and choice in terms of hypoglycemic agents for managing both type 1 and type 2 diabetes. The first of these new class of type 2 diabetes drugs to be approved by the FDA in 2005 was a glucagon-like peptide-1 receptor analogue (GLP1A), exenatide. Among other major classes of the newer generation drugs employed to manage type 2 diabetes are DPP-4 inhibitors, (also known as gliptins) that were approved in 2006 and sodium-glucose cotransporter-2 (SGLT2) inhibitors, the first of which was approved in 2013. Some of these drugs are also used for weight reduction alone (independent of diabetes) and have become extremely popular in this area. In addition, once-weekly basal insulin analogue Insulin (icodec) is becoming popular in some countries (although not available in the USA) and once-weekly combination of insulin icodec plus semaglutide (a GLP-1A) is likely to be available in the very near future.

Sufficient experience has accumulated to understand the perioperative implications of some of these drugs. While pulmonary aspiration is a major potential risk with GLP-1A, SGLT2 inhibitors can predispose to euglycemic keto acidosis. FDA has declined to approve icodec because of the risks of

 doi:10.20944/preprints202411.0253.v1

moderate-severe hypoglycemia. The current review will explore the existing research with regards to these drugs and their interactions, as it relates to anesthesia and perioperative management.

1. Glucagon-Like Peptide 1 Receptor Agonists

Glucagon is a polypeptide consisting of 29 amino acids in a single chain secreted by the alpha cells of the pancreatic islets. Glucagon stimulates glycogenolysis and gluconeogenesis, and with these two actions, plays an important role in glucose homeostasis (1). Glucagon-like peptide 1 (GLP1), on the other hand is a 30-amino acid peptide hormone produced in the lower intestinal epithelial endocrine L-cells that resemble pancreatic alpha cells, by differential processing of proglucagon (2,3). Along with glucose-dependent insulinotropic polypeptide, these two polypeptides are classified as incretins. Incretins are hormones that are secreted in response to the presence of food in the GI tract.

Proglucagon is the precursor of both glucagon and GLP1. In smaller amounts, GLP1 is also secreted in pancreas and central nervous system. As stated, it is primarily secreted in response to a meal (along with gastric inhibitory polypeptide from K-cells of the upper small intestine) and the secretion corelates with insulin secretion (4). An enzyme named dipeptidyl peptidase 4 (DPP-4) located on the luminal surface of the endothelial cells (white cells lining the capillary) destroys three fourths of GLP1 before it reaches portal circulation. Nearly half of the remaining is destroyed in the liver, so that, eventually only about 10–15% of the secreted GLP1 actually enters systemic circulation.

Among the multitude of actions of GLP1 are glucose-dependent stimulation of insulin secretion, slowing of gastric emptying, inhibition of food intake, increased natriuresis, reduction of blood pressure, neuroprotection and diuresis (5). Recently, it is also implicated in learning and memory, reward behavior, and palatability. It has cardio- and neuroprotective effects, decreases inflammation and apoptosis. As a result, GLP1 agonists have expanding role in clinical practice beyond the treatment of type 2 diabetes. These include Alzheimer's dementia, hypertension, dyslipidemia, non-alcoholic steatohepatitis, parkinsonism, infertility, polycystic ovarian syndrome, associative learning, stroke and even some types of cancer. They are increasingly used to treat New York Heart Association class III/IV heart failure (6). In these patients, they are shown to improve left ventricular function, functional status, and quality of life. In addition, major cardiovascular events seem to be lower in patients treated with GLP1 analogues. As a result, an anesthesia provider should expect to see patients being prescribed with these drugs for a wide variety of indications.

1.1. Perioperative and Anesthesia Implications

Since the approval of the first glucagon-like peptide-1 receptor analogue (GLP1A), exenatide, by the FDA in 2005, the market for GLP1A has exploded. Some of the popular GLP1A available in the market are Trulicity, Mounjaro, Wegovy, Zepbound, Saxenda and Victoza. According to Prophecy Market insights, the global GLP1A market size and share is projected to grow from USD 45.3 Billion in 2023 to reach USD 606.3 Billion by 2034 (7).

Of particular significance to the anesthesia providers is the ability of GLP1A to slow the stomach emptying. It is known to inhibit prandial gastrointestinal motility through myenteric neuronal mechanisms (8). It also decreases gastric acid secretion, GI transit, motility, and gastric wall tone (9–14). The gastric slowing effect is likely to be a vagal effect, as the effect is lost following vagal afferent denervation (15).

Many studies have quantified the delayed gastric emptying effects of GLP1A. These methods have included the use of radioactive tracers, acetaminophen-based absorption testing, stable isotope breath testing, esophagogastroduodenoscopy (EGD) and capsule studies.

1.1.1. Gastric Scintigraphy Studies

In a placebo controlled study, Stevens et al, assessed gastric emptying by scintigraphy in 15 volunteers on two occasions following 2 days dosing with sitagliptin (100 mg/day) or placebo (16). They did not find any difference in gastric emptying. Maselli et al, conducted a randomized, parallel-group, placebo-controlled, 16-week trial of liraglutide. Among other parameters, they measured

 doi:10.20944/preprints202411.0253.v1

gastric emptying of solids and gastric volumes (17). In their analysis, liraglutide prolonged both 50% and 25% gastric emptying compared with placebo (at 5 and 16 weeks) and increased satiety at 16 weeks. After 8 weeks of lixisenatide treatment, Rayner et al, observed sustained slowing of gastric emptying in type 2 diabetes patients (18).

1.1.2. Esophagogastroduodenoscopy Studies

However, more relevant for anesthesia providers would be studies involving retained gastric contents visualized during EGD. In a single center retrospective electronic chart review of 404 patients (of which 33 were on semaglutide) undergoing elective esophagogastroduodenoscopy, Silveira et al, found increased residual gastric content (RGC) in 8 (24.2%) in the semaglutide group and 19 (5.1%) in the non-semaglutide group (19). 12.2% of the patients were taking semaglutide for weight loss and the rest for type 2 diabetes. All the patients were appropriately fasting. In those with increased RGC, semaglutide was withheld for 10 (6–15) days. In those without increased RGC, it was withheld for 11 (7.75–12.5) days ($p = 0.54$). RGC was defined as any amount of solid content from the esophagus to the pylorus, or > 0.8 mL/Kg of fluid content as measured from the aspiration/suction canister. One patient in the semaglutide group sustained pulmonary aspiration, however the person had previous gastric bypass.

After investigating the patients taking GLP1 analogues (liraglutide, dulaglutide, semaglutide, and semaglutide) for diabetes, and undergoing EGD, Kobori at al, concluded that GLP1 analogues were associated with increased gastric residue (20). In this case-control study, that involved propensity score-matched comparison, GLP-1A group exhibited higher gastric residue that was statistically significant.

However, in another retrospective cohort study with matched controls, Stark et al, did not find that GLP1A significantly increased odds of retained food on EGD (21).

1.1.3. Meta-Analysis

HIramoto et al, conducted a meta-analysis that included fifteen studies. Of these, Five studies utilized gastric emptying scintigraphy, ten studies utilized the acetaminophen absorption test (22). They did not find any substantial differences in gastric emptying on modalities reflective of liquid emptying. Despite the fact that the administration of GLP1A was associated with higher gastric emptying half-time on scintigraphy ($T_{1/2}$) than placebo, its clinical impact was only limited. Considering that most patients presenting for elective procedures fast for 8-10 hours, the impact is be minimal or none.

1.2 Society Guidelines

Various anesthesia and gastroenterology societies have put forth their guidelines to assist clinicians in their practice (23–28).

American Society of Anesthesiologists (ASA) task force on preoperative fasting published their guidelines in June 2023. For elective procedures (surgical and non-surgical), the society recommends holding GLP-1 agonists on the day of the procedure/surgery (if the patient is taking daily). For those on once weekly dosing, the recommendation is to withhold a week prior to the procedure/surgery. This applies to patients taking their GLP-1 agonists for any indication. The guidelines from other anesthesia societies are similar. In a detailed, evidence supported communication to its members, American Gastroenterological Association (AGA), advised to exercise best practices when performing endoscopy on patients on GLP1A. The AGA argues that the ASA's "consensus-based guidance on perioperative management," is not based on sufficient and robust evidence. AGA argues that there is "No data to support stopping GLP-1 agonists prior to elective endoscopy".

Finding liquid/semisolid/solid contents in the stomach after esophageal intubation is not uncommon during EGD. Lin at al, studied practice patterns and outcomes of patients with retained gastric food content encountered during endoscopy (29). 4.1% (730 / 17,868) of the patients who underwent endoscopy at their facility (Loma Linda University Medical Center, California, USA), had

 doi:10.20944/preprints202411.0253.v1

retained gastric food content. All the patients were fasting at least 6 hours for solids and 2 hours for clear liquids. Exclusion of those with altered surgical anatomy or who were already mechanically ventilated before the procedure, left 629 (3.5%) patients. Of these, 506 received moderate sedation, while the remainder were sedated by an anesthesia provider or administered general anesthesia. 40 (6.4%) had respiratory adverse events including aspiration pneumonia. One patient had respiratory obstruction requiring mucosal plugging. Sadly, 21 (51.2%) required admission to the intensive care unit and mechanical ventilation, with 10 of them dying. As demonstrated in this and other studies, it is not uncommon to encounter retained gastric food in the stomach of patients presenting for EGD, which can lead to aspiration pneumonia (30–34). There are established risk factors such as gastroparesis and anesthesia providers do not intubate or delay such procedures on a routine basis.

In conclusion, the guidelines issued by the anesthesia societies seem to be a cautious approach to an evolving problem. The American diabetes association concedes that there is little data on the area of delayed gastric emptying in the perioperative period (35). While waiting for prospective studies in patients presenting for an endoscopy and evaluating the gastric contents, both in relation to length the patients were on the GLP1A and the duration of withholding, we agree that patients arriving for GI endoscopy should be treated differently. Those presenting for a combined EGD and colonoscopy, should have their EGD performed first. This provides an opportunity to carefully pass the endoscope into the stomach in a semi-sitting position. Any fluid contents can be suctioned, and the procedure/s can proceed. If solids/semisolids are seen, the planned procedures should be abandoned. Although, most hospitals have accepted and adapted the new advisory in terms of withholding these medications, patients can occasionally present to a procedure, either unaware of the recommendations or having forgotten to follow them. In such cases, it is important to explain the current state of knowledge/recommendations and adapt a prudent approach that best serves the needs of our patients. Extended fasting times in patients who present for colonoscopy or combined EGD/colonoscopy should provide additional layer of protection.

The most recent multi-society guidelines released on 29th October 2024, recommend a shared decision-making approach in consultation with procedural, anesthesia, and prescribing care teams balancing the need for the GLP-1A with individual patient risk (36). The guidelines' noted that the escalation phase of GLP-1A causes greater delay in gastric emptying. Additionally, higher doses and weekly dosing regimes are more likely to cause gastrointestinal side effects. In the absence of any inherent factors that slow gastric emptying, one might not withhold GLP-1A. Factors noted above such as preoperative liquid diet for at least 24 hours, (as recommended in patients undergoing colonoscopy and bariatric surgery) may be extended to other patients with intrinsic risk factors such as gastroparesis. Point-of-care gastric ultrasound to evaluate gastric contents should be utilized as appropriate.

2. Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, also called gliflozins, such as canagliflozin, dapagliflozin, and empagliflozin are popular in the treatment of both type 1 and type 2 diabetes (37–39). In addition, their role in the management of obesity and heart failure is acknowledged (40,41).

2.1. Mechanism of Action

The most recent physiology and pharmacology aspects of SGLT-2 inhibitors is extensively discussed by Ernest M Wright from the Department of Physiology, David Geffen School of Medicine at UCLA, Los Angeles, California (42). Typically, of 120–180 g of glucose filtered in the kidney every 24 hours, only 0.5 grams is excreted in the urine. SGLT2 receptors are principally found in the proximal convoluted tubule of the nephron (41). Nearly 95% of the filtered glucose is reabsorbed by these nephrons. The SGLT2 receptors are upregulated in patients with diabetes, further increasing the absorption. The remaining glucose is reabsorbed by the SGLT1 activity present in S3 segment pf the nephron, that consists of the remainder of the proximal straight tubule in the medullary ray and outer stripe of the outer medulla(43).

 doi:10.20944/preprints202411.0253.v1

By potent and selective SGLT-2 receptor inhibition, the gliflozins induce dose-dependent glucosuria in healthy subjects (44). However, even when working at their full therapeutic doses, they only decrease glucose reabsorption by 40–50%. As a result, even though a large portion of filtered glucose is normally reabsorbed by SGLT 2 receptor mediated action, the resulting glucosuria is modest, about 50–60 g in 24 hours(45). Efforts are being made to create SGLT1 inhibitors that can further increase glucosuria. Dual SGLT1/SGLT2 inhibitors such as sotagliflozin are available (46–49). It is approved for both heart failure and diabetes. However, the maximum glucose excretion reported with this drug is 44 grams. This is less than that reported with some SGLT2 inhibitors which could be as high as 60–70 grams per day.

Inhibition of SGLT-2 receptors is known to increase the plasma glucagon/insulin ratio in the fasted state in mice (50). SGLT-2 receptors are not expressed in pancreatic α- and β-cells in mice. However, they are expressed in human pancreatic α-cells. The cause of altered glucagon/insulin ratio is indirect and not related to direct effect on glucagon and insulin secretion.

2.2 Clinical Indications

2.2.1 Diabetes, Type 1 and 2

SGLT-2 inhibitors are used frequently in conjunction with other drugs such as metformin and glucagon-like peptide 1 receptor agonists (GLP1-A) in type 2 diabetes. However, newer indications are being added on a regular basis.

Use of SGLT-2 inhibitors in type 1 diabetes (T1DM) is relatively recent and is controversial (38). Their HbA_{1c}-lowering efficacy seems to be highest at 8-12 weeks of therapy and decreases with longer use. In addition, the risk of ketoacidosis increases with combined insulin- SGLT-2 inhibitors therapy (37). However, a meta-analysis of 16 RCTs consisting of 7192 patients with T1DM, found a reduction in the insulin requirements without an increased risk of hypoglycemia and diabetic ketoacidosis (38). However, in another meta-analysis of seven randomized trials encompassing 42,375 participants and 5 cohort studies encompassing 318,636 participants with type 2 diabetes, the SGLT2 inhibitors were found to increase the risk of ketoacidosis. Clearly, the risk of ketoacidosis should be explained to these patients.

2.2.2. Weight Loss

SGLT2 inhibitors are effective in facilitating weight loss on their own, and combining them with other agents provides additional benefit in some patients. Pratama et al, performed a systematic review of seven studies and concluded that SGLT2 inhibitors can cause significant weight loss in patients with obesity and without diabetes (51). Bays et al, evaluated the effect of canagliflozin, a SGLT-2 inhibitor in overweight and obese subjects over 12 weeks, at different doses (overweight and obese subjects) administered once daily. One of the side effects observed was higher rates of genital mycotic infections in women. Patients also experience significant weight loss at the end of first 2 weeks (52). Patients who are >70 years old, body mass index >25 kg/m^2 and those using sulfonylureas have better odds of losing weight (53). SGLT-2 inhibitors are demonstrated to reduce body weight and visceral adiposity in Asian patients with T2DM (54).

2.2.3. Heart Failure

In adults with type 1 diabetes, Sotagliflozin, a SGLT-2 inhibitor, when used as an adjunct to insulin therapy significantly reduced the predicted 5- and 10-year cardiovascular disease risk, possibly by reducing the body weight and blood pressure (55).

There is evidence to suggest that SGLT-2 inhibitors can prevent heart failure (HF) in patients with T2DM and decrease major adverse cardiovascular events and hospitalization for HF in patients with concomitant HF and T2DM (56,57). Dapagliflozin, a SGLT-2 inhibitor was shown to reduce the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and mildly reduced or preserved ejection fraction (58). This study included 6263 patients with heart failure and a left ventricular ejection fraction of more than 40%. A meta-analysis of 12,251 participants

 doi:10.20944/preprints202411.0253.v1

supported the benefits of SGLT-2 inhibitors in reducing the risk of cardiovascular death and hospitalizations in patients with heart failure irrespective of ejection fraction or care setting (59). Further, the beneficial effects of these drugs in heart failure seems to be a class effect (41). Some of the mechanisms could be indirect related to diuretic like effect, beneficial effects on calcium handling, decrease blood pressure and body weight; however there could be direct molecular mechanisms at play and these are being explored.

2.3. Perioperative Concerns with SGLT-2 Inhibitors

Inhibition of SGLT-2 receptors is known to increase the plasma glucagon/insulin ratio in fasting mice. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells is known to trigger glucagon secretion (60). In patients with T1DM, increased glucagon secretion contributes to the elevated ketones and acidosis present in diabetic ketoacidosis (61).

Patients presenting for elective surgical procedures routinely fast for varying periods of time, as per the recommendations of the ASA (62). In addition, patients presenting for colonoscopy fast for extended periods of time for semisolids and solids. Although recent changes have made the colonic prep more tolerable, the duration of avoidance of solids has stayed the same (63).

2.3.1. Case Reports of Ketoacidosis

Cases of euglycemic ketoacidosis in the perioperative period are reported across all specialties and in various perioperative settings (64–68). Mackintosh et al, reported a case of euglycemic ketoacidosis which presented as unexplained encephalopathy in the neurocritical care after resection of a left temporal meningioma (65). The 68-year-old woman with a history of type 2 diabetes mellitus had not taken empagliflozin the day of surgery, however the drug has a half-life of >12 hours. Biochemistry revealed blood glucose 140 to 160 mmol/L, bicarbonate 9 mmol/L, anion gap of 21, and pH of 7.2. Treatment with insulin was effective and restored the patient's neurological status to baseline.

Ritche et al, reported a case of intraoperative severe Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (EDKA) requiring treatment in the critical care unit in a patient undergoing surgery for intracapsular neck of femur fracture. The patient was on Empagliflozin 10 mg, once a day. In the operating room a severe high anion-gap metabolic acidosis (Base excess of – 22, pH of 6.96 and Ketones 4.9 mmol/L and normal lactate level) was noted. The patient was successfully managed with intravenous insulin and 0.9% sodium chloride (64) with inescapable morbidity due to delayed mobilization.

Kameda et al, reported ketoacidosis without elevated blood glucose in a 65-year-old woman with type Ⅱ diabetes and unstable angina who underwent a semi-emergency coronary artery bypass grafting. The SGLT2 inhibitor was stopped for more than 24 hours preoperatively (66).

Meyer et al, reported eight cases (aged between 45 and 75 years) of SGLT2i-associated EDKA in the setting of colonoscopy that occurred between August 2019 and February 2020 across three centers (69). Seven patients took SGLT2i up to the day prior and one took it on the morning of colonoscopy. Factors such as very-low-calorie diet, volume depletion (related to fasting and prep), reduced insulin administration/secretion are some of the purported factors.

Blau et al analyzed the data from FDA adverse event reporting system for reports of acidosis in patients treated with canagliflozin, dapagliflozin, or empagliflozin (70). They discovered 192 reports of ketoacidosis (of a total of 259 reports of acidosis) in patients on SGLT2 inhibitors. Chumbe et al, observed that the use of SGLT-2i at least a week prior to colonoscopy significantly increased the risk of ketoacidosis post procedure. FDA revised their drug label with warnings in September 2023 to include prolonged diabetic ketoacidosis and glucosuria (71,72).

2.4. Guidelines

In line with the FDA recommendations, American college of cardiology recommends that canagliflozin, dapagliflozin, and empagliflozin to be discontinued 3 days before scheduled surgery

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and ertugliflozin should be stopped at least 4 days prior to surgery (73). In the perioperative setting, EDKA should be considered when a patient has an anion gap metabolic acidosis and pH <7.3, elevated ketones in the blood or urine and blood glucose <200.

Australian diabetic society recommend that clinicians should consider DKA/ euDKA in patients taking SGLT2i and symptoms such as abdominal pain, nausea, vomiting, fatigue or metabolic acidosis with relatively normal plasma glucose, capillary blood ketone (or blood beta-hydroxybutyrate) levels >1.0 mmol/L with or without hyperglycemia and base Excess (BE) < -5mmol/l (74). Further, they recommended withholding SGLT2i at least 3 days pre-procedure for surgeries and procedures requiring one or more days stay in hospital, and/or requiring 'bowel preparation' including colonoscopy. For procedures such as esophagogastroduodenoscopy and other same day procedures.

American diabetes association (ADA) agrees that SGLT2 inhibitors should be avoided in cases of severe illness, in people with ketonemia or ketonuria, and during prolonged fasting and surgical procedures. In patients with heart failure, they may be initiated or continued during hospitalization and upon discharge, if there are no contraindications and after recovery from the acute illness. Further, regarding their use during perioperative period, the ADA advises to consider discontinuation of SGLT2 inhibitors 3–4 days before surgery (35).

At the time of writing, with reference to SGLT2 inhibitors, the ASA has not issued an official statement.

3. Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase IV (DPP-4) inhibitors or gliptins were the second among the new generation of antidiabetic drugs to be approved by the FDA. Sitagliptin Phosphate (Januvia, Merck) was approved in October 2006 (75).

3.1. Mechanism of Action

The enzyme DPP-4 is present in many tissues, and it is a membrane-bound serine proteinase (a type of protease) that removes dipeptides from the amino terminal end of peptides (76). In addition to incretin hormones such as GLP-1 and GLP-2, DPP-4 also cleaves growth factors, chemokines, and peptides (77). Incretins (e.g., GLP-1) stimulate insulin secretion and are secreted in response to food intake. As a result of this "incretin effect", oral intake of glucose produces a stronger (two- to three-fold higher) insulin secretory response compared to intravenous glucose administration(78). Inhibition of DPP IV activity followed by reduced peptide cleavage and increased endogenous incretin hormone activity is the main rationale of the use of gliptins in the treatment of type 2 diabetes (79). It is important to note that DPP-4 inhibitors have no intrinsic ability to lower glucose levels and carry no risk of hypoglycemia.

3.2. Clinical Benefits

The HbA1c lowering ability of DPP-4 inhibitors in patients with type 2 diabetes is studied extensively. In a meta-analysis of 43 randomized controlled trials, Esposito et al, found that greater proportion of type 2 diabetic patients can achieve the HbA1c goal <7% with DPP-4 inhibitors compared to placebo. In addition, there was no weight gain, or hypoglycemic risk (80). Another meta-analysis of eight RCTs of DPP-4 inhibitors and metformin (as initial combination therapy) or monotherapy in patients with type 2 diabetes, DPP-4 inhibitors were found to be safe and effective in controlling the blood glucose (81).

While comparing DPP-4 inhibitors with GLP-1 receptor agonists, it was noticed that the latter can lower cholesterol and weight while DPP-4 inhibitors produced only minor reduction of cholesterol and were weight neutral. On the positive side, DPP-4 inhibitors do not cause gastrointestinal side-effects such as nausea (82). They do not have cardiovascular benefits and in fact might cause congestive heart failure by degradation of B-type natriuretic peptide. In comparison to SGLT2i and GLP1 analogues, DPP-4 Inhibitors only produce modest reduction in A1c levels (0.5–

 doi:10.20944/preprints202411.0253.v1

0.8). Although DPP-4 inhibitors lack significant cardiovascular benefit in type 2 diabetes, for patients with T2DM, other than atrial flutter, they do not cause any major cardiac arrhythmias. In short, although their efficacy is less than GLP-1 receptor agonists and SGLT2i and lack concomitant extra diabetic benefits, they are relatively safe (83). Nasopharyngitis and skin lesions are some of the reported adverse effects, however, these are not serious enough to discontinue the treatment (82). Both DPP-4 inhibitors and GLP-1RAs are not known to pose any demonstrable risk of pancreatitis and pancreatic cancer (84).

3.3. Perioperative Concerns

The working party of the Association of Anaesthetists of Great Britain and Ireland allows DPP-4 inhibitors to be taken by the patient as normal both the day preceding and the day of the surgery. Those patients on variable-rate intravenous insulin infusion should stop DPP-4 inhibitors until eating and drinking normally (85). ADA does not endorse administration of DPP-4 inhibitors to hospital in patients (35).

4. Imeglimin

Imeglimin is the latest among the new classes of drugs employed in the treatment of diabetes. Although as yet not approved by the FDA, Imeglimin was approved in Japan in June 2021 and India in September 2022 (86).

4.1. Mechanism of Action

Imeglimin is structurally similar to metformin (87). It is synthesized from metformin by adding acetaldehyde to a solution of metformin hydrochloride, sodium hydroxide, and water (88). It is known to reduce blood glucose by two mechanisms. It amplifies glucose-stimulated insulin secretion and preserves the β-cell mass. It also enhances insulin action, inhibits liver glucose output, and improves insulin signaling in both liver and skeletal muscle. At the cellular level, it acts by modulating the mitochondrial function. More specifically, it competitively inhibits complex I of the respiratory chain while restoring the function of complex III (88).

4.2. Clinical Benefits

Imeglimin is seen as a valuable addition to T2DM treatment arsenal. In a Japanese phase 3, pivotal, open-label trial, patients with type 2 diabetes were prescribed with imeglimin 1000 mg twice-daily orally for 52 weeks as monotherapy or combination therapy (with one of the following:-α-glucosidase inhibitor, biguanide, dipeptidyl peptidase-4 inhibitor, glinide, glucagon-like peptide-1 receptor agonist, sodium-glucose co-transporter-2 inhibitor, sulphonylurea, or thiazolidinedione). The reduction in HbA1c was modest both as mono and oral combination therapy (0.46% and 0.56%-0.92%). The most effective HbA1c reduction occurred with DPP4-Inhibitor in combination with imeglimin (89). More importantly, no clinically significant changes in ECG, vital signs, physical examination, or laboratory tests were noted in any groups. The reduction in HbA1c improved significantly in poorly controlled type 2 diabetes when imeglimin was added to their insulin regime.

In a meta-analysis of eight RCTs, Abdelhaleem et al, found that imeglimin group was superior to the control group in controlling glycated hemoglobin and fasting plasma glucose ($P < 0.00001$). However, no benefits were noted with regards to lipid parameters, including triglyceride, LDL-C, and HDL-C and homeostasis model assessment of insulin resistance (HOMA-IR), a method for estimating insulin resistance (90). In another meta-analysis of three double-blind RCTs, Singh et al, found a significant reduction in HbA1c with imeglimin 1000 mg BID (compared to placebo), however, with high heterogeneity (86).

Imeglimin was safely used six patients with type 2 diabetes undergoing hemodialysis or peritoneal dialysis. There were no adverse effects such as hypoglycemia, diarrhea, nausea, or vomiting (91). Imeglimin has shown favorable effects on the development of plaque formation and progression of atherosclerosis in mice, in whom the atherosclerotic plaque formation was induced

 doi:10.20944/preprints202411.0253.v1

artificially by producing hyperglycemia with streptozotocin treatment (92). In mice studies, imeglimin was also shown to prevent heart failure while preserving ejection fraction (93).

4.3. Perioperative Concerns

Currently, there are no guidelines from any societies to guide the perioperative administration of imeglimin in patients presenting for elective surgery or their continuation/restarting during post operative period. Based on the available evidence, it is reasonable to stop it on the day of the surgery/procedure.

5. Insulin Icodec

Under the brand name, Awiqli®, insulin Icodec is approved for use in both type 1 and type 2 diabetes in the EU, Canada, Australia, Japan and Switzerland(94). FDA declined to approve the drug in its May 2024 meeting, pending submission of more information on the manufacturing process (95).

5.1. Mechanism and Chemistry

Insulin itself is not a novel treatment for diabetes management. However, it has been a struggle to find longer acting insulin preparations. While NPH insulin (Neutral Protamine Hagedorn) has a half-life of 5-10 hours and administered 1-2 times daily, 1st generation basal analogs and ultra long-acting basal insulin analogs have half-lives of 0.5 and 1 day and can be administered once daily. More frequent need for injections invariably results in poor compliance and subsequent poor diabetes control in both type 1 and type 2 diabetes. Poor compliance in turn results in recurrent diabetes ketoacidosis. The most recent version is once-weekly icodec, with a half-life of about 1 week can increase compliance. It has a fatty acid side chain that is responsible for its prolonged duration of action. Insulin icodec was made by re-engineering the ultra-long oral basal insulin OI338 (96).

5.2. Efficacy and Adverse Effects

In a multicenter, open-label, treat-to-target phase 2 RCT involving type 2 diabetes patients (HbA_{1c} 7.0–10.0%) on basal insulin (total daily dose 10–50 units),3 groups were studied. They were icodec with an initial 100% loading dose (and double first dose), icodec with no loading dose and insulin glargine 100 units once daily, for 16 weeks (97). Switching to once-a-week icodec resulted in effective glycemic control.

In a meta-analysis that included four RCTs, (published from 2020 to 2023) involving 1035 patients with type II diabetes, Saleem compared Insulin Glargine U-100 and Insulin Icodec. They recorded similar mean changes in HbA1c (%) and FPG (mg%) (98). Significantly, there was no significant difference in hypoglycemic episodes.

Mukhopadhyay included seven trials in a meta-analysis comparing once-daily basal insulin analogs to once-weekly basal insulin icodec. They found a slightly higher risk of overall hypoglycemia and weight gain, without any difference in severe hypoglycemia with once-weekly basal insulin icodec. Both groups had similar HbA1c control (99).

5.3. Perioperative Implications

The FDA expressed the concern with hypoglycemia in its May 2024 committee meeting. Based on the submitted datasets, the FDA safety statistical reviewer concluded that the incidence of Level 2 and Level 3 Hypoglycemia in the phase 3 trials were unacceptably high (100). As described by the endocrine society, a blood sugar of less than 70 mg/dL but more than 54 mg/dL is labelled as Level 1 (mild) hypoglycemia. A level 2 (moderate) hypoglycemia is less than 54 mg/dL. A level 3 (severe) hypoglycemia is also less than 54 mg/dL; however, the person is unable to function because of mental or physical changes due to low blood glucose and requires assistance from another person for recovery because they are confused or unconscious (101,102). Anesthesia providers need to be cognizant about the higher possibility of unexpected and serious hypoglycemia in patients on insulin

 doi:10.20944/preprints202411.0253.v1

icodec. The product monograph warns about the hypoglycemia risks, especially while changing from other insulins to Awiqli® (103).

There are no specific guidelines available with regards to the perioperative management of caring for patients on insulin icodec.

Table 1 lists all the modern hypoglycemia agents and their perioperative implications.

Table 1. Modern hypoglycemia agents and their perioperative implications.

Drug Class/Drugs	Perioperative implications	Current recommendation
Glucagon-like peptide 1 analogs (GLP 1 A	Delayed gastric emptying, increased risk of aspiration	AGA, ASMB, ASA, SAGES, ISPCOP jointly recommends a shared decision-making approach- consult procedural, anesthesia, and prescribing care teams balancing the need for the GLP-1A with individual patient risk. Point-of-care gastric ultrasound, if necessary. If no additional risk factors (e.g., gastroparesis), no need to withhold before the surgery/procedure. Recognize need for modified/extended fasting in some situations
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	ACC recommends withholding 3 days before surgery (for canagliflozin, dapagliflozin, and empagliflozin) and 4 days prior to surgery (for ertugliflozin). ADA recommends avoiding in cases of severe illness, in people with ketonemia or ketonuria, and during prolonged fasting and surgical procedures
DPP-4 inhibitors	Atrial flutter reported in patients with patients with T2DM	DPP-4 inhibitors can be taken as normal both the day preceding and the day of the surgery; patients on variable-rate intravenous insulin infusion should stop DPP-4 inhibitors until eating and drinking normally . (working party of the AAGBI). DPP-4 inhibitors should not be administered to hospitalized patients (ADA)
Imeglimin	Appears to be safe	Currently, there are no guidelines. Reasonable to avoid on the day of the procedure
Insulin Icodec	Increased risk of moderate and severe hypoglycemia	Currently, there are no guidelines.

AAGBI- Association of Anaesthetists of Great Britain and Ireland, ADA- American Diabetic Association; T2DM- Type 2 diabetes mellitus, AGA-American Gastroenterological Association, ASMB-American Society for Metabolic and Bariatric Surgery, ASA-American Society of Anesthesiologists, SAGES-Society of American Gastrointestinal and Endoscopic Surgeons, ISPCOP-International Society of Perioperative Care of Patients with Obesity; ACC0 American college of cardiology.

6. Conclusions

The availability of multiple drugs with different mechanisms of action is a boon for patients with diabetes. Many of these drugs have benefits beyond the control of blood sugar alone. Delayed gastric emptying is the major perioperative concern in patients on GLP 1 analogs, while euglycemia ketoacidosis is the worry in patients on SGLT2 inhibitors. Fortunately, DPP-4 inhibitors and imeglimin do not have any known risks. The most recent iteration of insulin, icodec, is very

 doi:10.20944/preprints202411.0253.v1

promising. However, it has slightly higher risk of moderate and severe hypoglycemia. Various societies have published guidelines to address some of the concerns with GLP 1 analogs and SGLT2 inhibitors. While, more guidelines are anticipated, it is to be anticipated that other drugs might emerge. Novo Nordisk announced that phase 3a trial of IcoSema (once a weekly injection of combined semaglutide (a GLP1 analog) and icodec is completed in patients with type 2 diabetes (104). It is crucial that perioperative care providers are aware of both existing and upcoming developments in the field of diabetes to provide best experience to our patients.

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