



## Recent antidiabetic drugs and anaesthetic concerns

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### ABSTRACT

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. India remains as the diabetic capital of the world. With such prevalence of the disease, more patients are likely to come for anaesthetic interventions. A few classes of drugs like incretin mimetics, dipeptidyl peptidase inhibitors (DPP4 inhibitors), the sodium glucose cotransporter 2 inhibitors (SGLT2i) and a Colesevelam, a second-generation bile acid sequestrant have been recently introduced for the control of the disease. The incretin mimetics and DPP IV inhibitors are having a better safety profile with regard to a perioperative setting. Colesevelam with its gut mediated action may not be ideal in patients with abdominal surgeries. SGLT2i are a new class of drugs with effective glycemic control but are basically ketogenic with a lot of anesthetic implications. Out of the newer drugs, only SGLT2i group of drugs need to be stopped 1 – 2 days prior to surgery. The knowledge of newer drugs and their effects on various systems becomes indispensable for practicing anaesthesiologists.

**Keywords:** diabetes mellitus, drugs, anesthesia

### INTRODUCTION

Diabetes mellitus has classically been defined as a group of metabolic diseases with hyperglycemia as the most important finding due to defects in insulin secretion, insulin action, or a combination of both. The majority of diabetic cases can be classified either as type 1 or type 2 diabetes. As type 2 diabetes is more common, we will restrict ourselves to oral drugs for type 2 diabetes in this short narrative review. According to World Health Organization (WHO), India had 69.2 million people living with diabetes in 2015. Nearly 98 million people in India may have type 2 diabetes by 2030.<sup>1</sup> Recently the number of patients coming for surgery with diabetes mellitus is increasing many folds. Treatment modalities for diabetes include drugs, nutrition,

lifestyle changes and insulin. With metformin invented about 60 years ago, still in active use, there are many other drugs which include sulfonyl ureas, glitazones, repaglinides, acarbose, voglibose etc. There are certain hiccups with older drugs, which include hypoglycaemia, beta cell dysfunction, gastric bloating and bone fractures. Still in a community assessment of control of diabetes mellitus, it's found to be unsatisfactory<sup>2</sup>. Hence, it's the custom of medical science which goes on to invent newer drugs and avoids certain side effects probably with better efficacy. We have a few new classes of drugs like incretin mimetics, dipeptidyl peptidase inhibitors (DPP4 inhibitors), the sodium glucose cotransporter 2 inhibitors (SGLT2i) and a Colesevelam, a second-

generation bile acid sequestrant<sup>3</sup>. Hence more diabetics present to anaesthesiologists with such drugs and the knowledge about the same becomes essential. In this narrative review, we will try to present the effects, side effects of newer drugs with a special concern for the perioperative period.

### **Diabetes and perioperative stress:**

The stress of surgery and anaesthesia definitely alters the precisely regulated balance between hepatic glucose production and utilization of glucose in peripheral tissues. An upward surge in the secretion of counter regulatory hormones with perioperative stress (catecholamines, cortisol, glucagon, and growth hormone) causes release of inflammatory cytokines including tumor necrosis factor- $\alpha$ , interleukin-6 and interleukin-1 $\beta$ <sup>4</sup>. These processes can result in a defective state of insulin action, leading to a relative state of insulin resistance which is most significant on the first postoperative day and may persist even for three weeks following surgery.<sup>5</sup> The type of anaesthesia also influences the hyperglycemic response during surgery. General anaesthesia is frequently associated with more hyperglycemia and higher levels of catecholamines, cortisol and glucagon than either local or epidural anaesthesia.<sup>6</sup> With this basic idea of stress and anaesthesia, let us discuss the individual drugs and their significance in the perioperative period.

### **Incretin mimics:**

There is a factor from the intestine which stimulates insulin secretion as a response to oral glucose. This factor is named as incretin. It is a hormone released by the intestine due to ingested food especially those which contain carbohydrate and fat. Currently, there are two types of incretins which have been identified as Glucose dependent insulinotropic polypeptide (GIP) and Glucagon like peptide-1 (GLP-1). These two hormones act by triggering insulin release immediately after food intake, inhibiting glucagon secretion, delaying emptying of the stomach and possibly suppressing hunger sensation. These incretins are metabolized by dipeptidyl peptidase 4 (DPP IV). The incretin effect is defined as the increased stimulation of insulin secretion by oral when compared with intravenous administration of glucose under similar plasma glucose levels. To make it clear, when a person is given oral glucose to make a random plasma glucose of 175 mg%, he is

likely to have more insulin secretion than a person who measured the same 175 mg% with intravenous glucose. Indeed, patients with type 2 diabetes have been demonstrated to exhibit an almost total loss of this incretin effect. Several in-vitro studies have demonstrated that these incretins may increase the proliferation of pancreatic beta cell. There is a decrease of GIP function and GLP-1 amount in type-2 diabetes mellitus. An attempt should be made to increase both incretin hormones by using GLP-1 agonist and DPP-IV inhibitor. Currently, there are two approaches of incretin utilization as one of type-2 diabetes mellitus treatment, which is the utilization of incretin mimetic/agonist and DPP-IV inhibitor. Glucagon-like peptide-1 (GLP-1) agonists have recently been included in guidelines for the outpatient management of type 2 diabetes mellitus. GLP 1 agonists stimulate pancreatic insulin secretion but reduce glucagon secretion in a glucose dependent manner, especially with a lower risk of inducing hypoglycaemia. They have proven benefits in lowering postoperative blood glucose levels and hence potentially could be of value in the perioperative period.

### **Liraglutide:**

Liraglutide is a GLP 1 agonist. administered routinely once a day by subcutaneous injection, independent of meals, at any time of day. To improve gastro-intestinal tolerability, the usual starting dose is 0.6 mg liraglutide daily. After a week, the dose should be increased to 1.2 mg/day. Some patients may benefit from an additional increment to the maximum recommended daily dose of 1.8 mg. Daily blood glucose monitoring is not required usually, although may be considered if liraglutide is used with a sulphonylurea (SU). Treatment is contraindicated in patients with known hypersensitivity to liraglutide. Liraglutide slows gastric emptying, but does not interact with acetaminophen, there is a minimal risk of hypoglycaemia with an increased incidence of nausea and vomiting. In a study by Polderman et al<sup>8</sup>, they concluded that the pre-operative administration of liraglutide stabilised peri-operative plasma glucose levels and reduced insulin requirements, making this drug an interesting option for glycaemic control during non-cardiac surgery<sup>7</sup>. There is an increased incidence of nausea and vomiting with the use of this drug but in this study it is not statistically significant.

But the authors have recommended the use of drug after the induction of anaesthesia.

#### **DPP IV inhibitors:**

Dipeptidyl peptidase 4 inhibitors (DPP4i) are the class of drugs which act by preventing breakdown of endogenous gastric inhibitory polypeptide and glucagon-like peptide-1 (GLP- 1). Vildagliptin, Lina gliptin, Sitagliptin, Saxagliptin are some examples of this class of DPP4i drugs. They have a low risk of hypoglycemia. DPP-4 inhibitors were proven to be safe in a recent randomized trial of medical and non-cardiac surgery patients with type 2 diabetes treated at home with diet, oral antidiabetic agents, or a low daily insulin dose ( $\leq 0.4$  units/kg/day). *DPP-4 inhibitors may be taken the day of surgery and continued into the perioperative period.* One safety concern involves the potential possibility of DPP-4 inhibitors to interfere with the immune functions with an increased risk for infection (e.g. nasopharyngitis and urinary tract infection) and headache<sup>9</sup>. This drug may interact with digoxin, sulfa drugs, monoamine oxidase inhibitors (MAOIs), probenecid, non-steroidal anti-inflammatory drugs (NSAIDs and beta-blockers). The common side effects of sitagliptin are nasal stuffiness, nausea, diarrhoea which should be kept in mind.<sup>10</sup> The sore throat associated with the drug should be documented before airway manoeuvres. Hence from the overall findings, we could come to the conclusion that it's one of the good perioperative drug.

#### **Colesevelam:**

Colesevelam is a selective second-generation bile acid sequestrant. In addition to lowering LDL cholesterol levels which is its primary target, it is also used as an adjunct therapy for glycaemic control in a few adults with Type 2 diabetes. Compared with the earlier generations of bile acid sequestrants, colesevelam has better tolerability, lesser adverse effects and fewer potential drug interactions. The major drawback in developing countries is its present cost, many times the cost of sulfonyl ureas. The

reported adverse effects with this drug are mainly confined to two systems.i.e. gastrointestinal and metabolic. The patients with motility disorders of the gastrointestinal system may experience worsening dysphagia, oesophageal obstruction, constipation and hypoglycemia<sup>11</sup>. In cases of gut disorders, the treatment option may be changed to other hypoglycemic drugs. As there are no significant hypoglycemic episodes, this drug need not be stopped in a perioperative care setting.

#### **Sodium glucose cotransporter-2 (SGLT2) inhibitors:**

Normally, glucose is filtered from the blood into the kidneys and is then reabsorbed back in the S1 segment of the proximal tubule. This normal glucose reabsorption of the kidneys allows the body to decrease glucose loss and conserve calories. The glucose transporter-2 and sodium glucose cotransporter-2 (SGLT2) are responsible for approximately 90% of the glucose reabsorption in the kidneys. A newer class of oral anti hyperglycemic agents, called sodium glucose cotransporter-2 (SGLT2) inhibitors (SGLT2in), frequently called as "gliflozins" or "glucoretics," reduce blood glucose by promoting urinary glucose excretion through inhibition of SGLT2 channels located on the luminal side of the renal proximal tubules. These are marketed as oral drugs for diabetic control. The most common gliflozins are dapagliflozin, empagliflozin and canagliflozin. The most important advantage of these groups of drugs is their action being independent of insulin. The possible non glyceemic actions are decreased arterial stiffness, increased myocardial contractility and with less chances of cardiac rhythm disturbances. This class of drugs also decrease systolic blood pressure by 4 to 6 mm Hg approximately and diastolic pressure by 1 to 2 mm Hg even in normotensive and hypertensive type 2 diabetics. The impact on internal milieu by such drugs and anaesthetic manipulations can be tabled below.<sup>12</sup>

**Table 1 showing Sodium glucose cotransporter-2 (SGLT2)<sup>13,14</sup> inhibitors and perioperative concerns**

<b>Role of the drug</b>	<b>Possible anaesthesia implications</b>
Risk of hypoglycaemia	Strict vigil needed. Repeated measurements needed. Adjustments for tight control in major surgeries should be meticulous.
Volume contraction and hypotension	Hemodynamic instability as such is not very significant in healthy patients but to be cautious in potentially hypotensive drugs like propofol. Contrast agents should be administered with caution with volume depletion. Position changes, creation of pneumoperitoneum with their possible hemodynamic alterations may be more with concurrent use of this drug.
There is a chance of hyperkalemia	To be careful in patients with ACE inhibitors and mild renal insufficiency. Cautious use of drugs which cause hyperkalemia like succinyl choline.
The drug is ketogenic.	The surgery and anaesthesia are ketogenic. Major operative procedures and related fasting timings should be strictly supervised.
Diabetic ketoacidosis with blood sugars less than 300 are reported.	Euglycemic DKA and its fluid problems should be kept in mind. Any unwell patient on such drugs, assess blood gases.
Increased chances of genito urinary infections.	Clinicians should inquire about the potential of genital and urinary tract mycotic infections in patients taking SGLT2is.
Postoperative fluid and metabolic disturbances	There should be no rush to restart SGLT2i therapy postoperatively, until the patient is feeling well and eating normally

**Conclusion:**

There are a lot of investigational drugs like teplizumab but still not available in the market. More and more such drugs are going to flood the market in the next decade. Hence, as anaesthetists, we may encounter diabetic patients on newer drugs coming for differing surgeries. With the development of newer target receptors and drugs, it is necessary for us to update their perioperative implications.

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