Patients With Type 2 Diabetes: Anesthetic Management in the Ambulatory Setting: Part 2: Pharmacology and Guidelines for Perioperative Management

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Type 2 diabetes is a disease of metabolism in which the afflicted patient cannot properly utilize carbohydrates, fats, and proteins. Because the prevalence of type 2 diabetes is rapidly increasing throughout the general population, anesthesia providers must realize that a significant percentage of their patients will present with the disease. Anesthesia providers should have an intimate knowledge of the comorbidities and complications that are associated with type 2 diabetes and know the specific pharmacokinetics and pharmacodynamics of the drugs used to treat the disease. Part 1 of this series on the anesthetic management of type 2 diabetes in the ambulatory theater addressed the pathology of diabetes and its comorbid disease states. Part 2 of the series now focuses on the pharmacology associated with the many medications used to treat the disorder and the most recent guidelines for blood glucose management recommended for patients in an ambulatory surgery setting.

Key Words: Type 2 diabetes; Antidiabetic medication; Insulin therapy; Hypoglycemia; Hyperglycemia.

There are many different classes of antidiabetic medications and types of insulin currently in use to treat diabetes. It is important that the ambulatory anesthesia provider recognize the different classes of drugs, have a general understanding of their mechanism of action, and have specific knowledge of whether they should be taken prior to surgery.

Before any discussion of type 2 diabetic medications, it is prudent to recognize the importance of lifestyle modification in the treatment of diabetes. The cornerstone of any effective treatment regimen should include healthy eating, weight control, and physical activity; medications are always secondary.¹ When lifestyle changes alone are not sufficient to improve blood glucose levels, oral medications, with or without insulin, are the next logical step in treatment. These drugs will be discussed in groups or classes. The following are the 7 most common classes of drugs in current use for the

treatment of hyperglycemia associated with type 2 diabetes.

Sulfonylureas are the oldest class of oral antihyperglycemic agents; they were first introduced in the 1950s.² As such, there is vast experience with their usage. Sulfonylureas work by blocking potassium channels, which causes an influx of calcium into the pancreatic beta cells.³ The result is an increase in insulin release, assuming that there are a sufficient number of functional beta cells present, which may effectively control glucose levels by lowering hemoglobin A_{1c} levels by 1–2%.^{1,4} Side effects of sulfonylureas include hypoglycemia (especially when taken with aspirin), weight gain, hunger, and gastrointestinal upset.³ There is also evidence that sulfonylureas may increase the risk of cancer-related mortality.⁵

Biguanides are by far the most common oral antidiabetic drugs in current use. Metformin, the only remaining drug in this class, is the initial drug of choice in most type 2 diabetic treatment regimens.⁶ Metformin has 4 modes of action: (a) improving insulin sensitivity in tissues, (b) increasing peripheral glucose uptake, (c) decreasing gluconeogenesis in the liver, and (d) decreasing absorption of glucose in the small intestine.³ Metformin has advantages over the sulfonylureas in

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that it does not cause hypoglycemia or weight gain. In addition, metformin reduces hyperglycemia by approximately 25% in 90% of patients taking the drug.⁷ Biguanides may cause significant gastrointestinal upset and should not be used in patients with advanced renal disease (creatinine clearance of less than 50 mL/min) because of the risk of lactic acidosis.⁸ Metformin may also be prescribed for patients with polycystic ovarian syndrome.

Thiazolidinediones (TZDs) work by increasing insulin sensitivity in liver, adipose, and skeletal muscle tissues.¹ In addition to targeting insulin resistance, TZDs effectively work by increasing pancreatic beta cell insulin secretion. They are often used concurrently with sulfonylureas and biguanides to improve lipid metabolism, lower blood pressure, and reduce triglyceride levels.⁹ Disadvantages of TZDs include their extended amount of time to effective onset (30–60 days).⁸ Because they may cause peripheral and pulmonary edema, TZDs are contraindicated in patients with heart failure.¹⁰ There is evidence that TZDs may decrease bone density and thereby increase the risk of fractures, especially in women.¹¹ Increased risk of bladder cancer, hepatotoxicity, and macular edema have been reported in patients using TZDs. Former concerns surrounding myocardial infarction risks have largely been repudiated.¹²

Meglitinides work by increasing the amount of insulin secreted by the pancreas during the early phase of insulin release.¹³ Taken shortly before meals, these drugs are effective for rapid, short-term glycemic control with a peak onset of action of approximately 60 minutes and duration of action of approximately 4–5 hours.^{3,14} The use of meglitinides may cause slight weight gain; however, there is no associated diarrhea or gastrointestinal upset. Meglitinides may be substituted for biguanides in patients who cannot tolerate the side effects of metformin.¹³

Alpha-glucosidase inhibitors include acarbose and miglitol. They work by reducing gastric absorption of carbohydrates rather than stimulating insulin secretion or sensitivity and are therefore not as effective as other antidiabetic drugs.¹⁵ They are not commonly used in the United States because of the significant flatulence and diarrhea they may cause.

Since 2005, another class of drugs has been used for glycemic control by targeting the incretin system. Incretin hormones, glucagon-like peptide and gastric inhibitory peptide, are released by endocrine cells in the intestines during mealtimes.¹⁶ The incretin hormones cause an increase in insulin secretion by stimulating beta cells and a decrease in glucagon secretion by inhibiting alpha cells.¹⁷ These hormones are inactivated by dipeptidyl peptidase-4. Orally administered dipeptidyl peptidase-4 inhibitors, therefore, prolong the natural

hypoglycemic effect of the incretin hormones.¹⁸ Glucagon-like peptide agonists are also available, but only as injectable drugs. Newer analogs allow for once-weekly subcutaneous dosing, eliminating the twice-daily dosing that previously limited their use. Side effects of drugs that affect incretins include an increased risk of nausea, weight loss, and pancreatitis.⁸

In 2013, the US Food and Drug Administration approved the use of canagliflozin, the first of the sodium-glucose cotransporter (SGLT2) inhibitors for the treatment of type 2 diabetes.¹⁹ SGLT2 inhibitors work by increasing urine loss of glucose, reducing hemoglobin A_{1c} levels by approximately 0.5–1.0%.²⁰ They also increase the clearance of serum sodium, thus reducing peripheral edema, systolic blood pressure, and weight gain.²⁰ In 2015, the Food and Drug Administration warned that SGLT2 inhibitors may lead to ketoacidosis, urinary tract infections, and foot/leg amputations.²¹

According to the Society for Ambulatory Anesthesia's (SAMBA's) consensus statement on blood glucose management, no oral or noninsulin injectable antidiabetic drugs should be taken on the day of surgery. However, these drugs should not be discontinued the day prior to surgery.^{22,23} For patients who have renal insufficiency, metformin may be discontinued 24–48 hours before surgery, although some providers choose to withhold the drug from all patients prior to general anesthesia where renal perfusion may be compromised by anesthetic agents. SAMBA recommends that post-surgical oral and noninsulin injectable medication regimens be restarted only after normal food intake is resumed.²² This may be of significance for anesthesia providers who provide services for dental and oral surgery patients. For a list of prototypical antidiabetic medications and their respective classes, see Table 1.

INSULIN THERAPY GUIDELINES

Insulin therapy is required for all patients with type 1 diabetes. In type 2 diabetic patients, insulin therapy is often used in combination with oral antidiabetic drugs or after oral antidiabetic drugs are no longer effective.²⁴ Typically, a single dose of long-acting insulin is initially added to a patient's regimen of oral hypoglycemic agents.

Insulins are usually divided into 4 classes: (a) short and rapid-acting, (b) intermediate-acting, (c) long-acting, and (d) mixed insulins (Table 2). Controversy still exists concerning how insulin regimens should be altered for diabetic patients prior to surgery. All professional organizations agree that short-acting or rapid-acting insulin should be withheld on the morning

Table 1. Prototypical Antidiabetic Medications and Their Classes*

<i>Class</i>	<i>Prototypical Drug</i>	<i>Brand Names</i>
1. Sulfonylureas	Glyburide	DiaBeta, Micronase, Glynase, Glycron
	Glipizide	Glucotrol
	Glimepiride	Amaryl
2. Biguanides	Metformin	Glucophage, Glumetza, Fortamet
3. Thiazolidinediones	Rosiglitazone	Avandia
	Pioglitazone	Actos
4. Meglitinides	Repaglinide	Prandin
	Nateglinide	Starlix
5. Alpha-glucosidase inhibitors	Acarbose	Precose
	Miglitol	Glyset
6. Incretin mimetics		
GLP-1 agonists	Exanatide	Bydureon, Byetta
	Liraglutide	Victoza, Saxenda
DPP-4 inhibitors	Saxagliptin	Onglyza
	Sitagliptin	Januvia
	Vildagliptin	Glavus, Zomelis
	Linagliptin	Tradjenta
7. SGLT2 inhibitors	Canagliflozin	Invokana
	Dapagliflozin	Farxiga
	Empagliflozin	Jardiance

* GLP-1 indicates glucagon-like peptide; DPP-4, dipeptidyl peptidase-4; and SGLT2, sodium-glucose cotransporter.

of surgery. In the case of waking hyperglycemia, a short-acting or rapid-acting insulin dose should be guided by the anesthesia provider. Long-acting insulins, which are generally dosed at bedtime, should be taken at 75–100% of the usual dose.²² SAMBA has suggested that intermediate-acting insulins, such as neutral protamine hagedorn (NPH) insulin, should be taken at 75% of the evening dose the day prior to surgery.^{22,23} Mixed and intermediate-acting insulin doses should then be taken in the morning at 50% of the usual dose. The decision on dosing intermediate and long-acting insulin is ideally made with knowledge of the patient's typical waking blood glucose level to prevent hypoglycemia as well as unwanted hyperglycemia. The patient should check his or her blood glucose in the morning upon waking. If blood glucose levels are low, glucose containing clear fluids can be taken up to 2 hours before surgery and anesthesia. If hyperglycemia is present, the anesthesiologist should be contacted for appropriate insulin dosing.

Insulin pumps should generally be set at the “sick day” or “sleep” basal rates on the day of surgery²³ (Tables 2 and 3).

TREATMENT OF HYPOGLYCEMIA

In the conscious patient, hyperglycemia and hypoglycemia are usually easy to recognize. Chronic hyperglycemia classically presents as fatigue, vision disturbances, nausea, excessive thirst, and polyuria.²⁷ These patients generally appear in poor condition. Acute hypoglycemia usually presents with behavioral changes, such as confusion or combativeness, in addition to weakness, fatigue, sweating, and palpitations.²² Unfortunately, these signs of glycemic imbalance are difficult, if not impossible, to appreciate in a sedated or generally anesthetized patient. Because acute hypoglycemia can lead to brain failure and death, blood glucose levels in

Table 2. Management of Preoperative Insulin Therapy

<i>Insulin Regimen</i>	<i>Day Before Surgery</i>	<i>Day of Surgery</i>
Insulin pump	No change	“Sick day” or basal “sleep” rate
Short and rapid-acting	No change	hold dose
Intermediate-acting	No change for daytime dose, 75% of evening dose based waking blood glucose levels	50% of morning dose
Mixed insulin	No change	50% of morning dose
Long-acting	75–100% of night dose based on waking blood glucose	75–100% of morning dose (if taken)

Table 3. Insulin Types and Pharmacokinetics*^{25,26}

Type	Generic Name	Brand Name	Onset	Peak	Duration
Rapid-acting	Aspart	Novolog	10–20 min	40–50 min	3–5 h
	Lispro	Humalog	15–30 min	30–90 min	3–5 h
	Glulisine	Apidra	20–30 min	30–90 min	1–2.5 h
Short-acting	Regular insulin	Humulin (R)	30 min–1 h	2–5 h	5–8 h
		Novolin (R)	30 min–1 h	2–5 h	5–8 h
		Velosulin (R)	30 min–1 h	1–2 h	2–3 h
Intermediate	NPH	Humulin (N)	1–2 h	4–12 h	18–24 h
		Novolin (N)	1–2 h	4–12 h	18–24 h
Long-acting	Glargine	Lantus	1–1.5 h	n/a	20–24 h
	Detemir	Levemir	1–2 h	6–8 h	up to 24 h
Very long-acting	Degludec	Tresiba	30–90 min	n/a	42 h
Mixed		Novolog 70/30	10–20 min	1–4 h	up to 24 h
		Humalog 75/25	15 min	30 min–2.5 h	16–20 h
		Humulin 70/30	30 min	2–4 h	14–24 h
		Novolin 70/30	30 min	2–12 h	up to 24 h
		Humalin 50/50	30 min	2–5 h	18–24 h

* R indicates regular; NPH, neutral protamine hagedorn; and N, neutral.

diabetic patients receiving anesthesia must be monitored more vigilantly than in the nondiabetic patient.²⁸ Intraoperative hypoglycemia is of special concern in type 2 diabetics because they may have an impaired glucose counterregulation system, causing them to suffer symptoms of low blood glucose at higher levels than normal.²² Generally, though, hyperglycemia is the concern in type 2 diabetics. Typically, signs and symptoms of hypoglycemia are manifest when blood glucose levels drop to 45–55 mg/dL (2.5–3.1 mmol/L).²⁸ Therefore, in the anesthetized diabetic patient, 70 mg/dL (3.9 mmol/L) of blood glucose should be used as a trigger value for treatment to begin.²²

Oral glucose is most often given to a conscious hypoglycemic patient in the form of sugary drinks, glucose tablets, or gel. As a general rule of thumb, a conscious patient who has a blood glucose level less than 70 mg/dL (3.9 mmol/L) should consume 15 g of fast-acting carbohydrates. More complex carbohydrates, such as those found in candy bars, may require more time to raise blood glucose levels. Patients with a blood glucose level less than 50 mg/dL (2.8 mmol/L) should eat 30 g of fast-acting carbohydrates. This should raise blood glucose to an acceptable safe range²⁹ (Table 4). One gram of ingested glucose will generally cause blood glucose to rise about 5 mg/dL (0.28 mmol/L) for a 45-kg (100-lb) patient, 4 mg/dL (0.22 mmol/L) for a 68-kg (150-lb) patient, and 3 mg/dL (0.17 mmol/L) for a 91-kg (200-lb) patient. For instance, if a 68-kg (150-lb) patient had a blood glucose level of 70 mg/dL (3.9 mmol/L) and ingested 15 g of glucose gel, the patient's blood glucose would raise to approximately 130 mg/dL (7.2 mmol/L). Three glucose tablets containing 4 g of glucose each will raise a 91-kg (200-lb) patient's blood glucose level from

65 mg/dL (3.6 mmol/L) to approximately 100 mg/dL (5.6 mmol/L).

For unconscious patients, intravenous administration of 50 mL of dextrose 50%, or, if time allows, 500 mL of dextrose 5% (both delivering 25 g of dextrose), will have a similar effect on hypoglycemia and raise blood sugar approximately 75–125 mg/dL (4.2–6.0 mmol/L), depending upon the patient's weight. Of course, attention must be directed to the airway to ensure adequate ventilation and oxygenation. Cardiovascular collapse is a late sign of hypoglycemia. Dextrose solutions must be available for intravenous-trained dentists. Unconscious patients who do not have an intravenous line can be given 1 unit (1 mg) of glucagon subcutaneously. The dose of glucagon is generally halved for pediatric patients. For unconscious patients in hypoglycemic shock being treated by the non-deep sedation/general

Table 4. Foods That Contain Approximately 15 g of Fast-Acting Carbohydrates^{29–31}

Type	Serving Size
Beverage	118 mL (0.5 cup) apple juice
	118 mL (0.5 cup) orange juice
	118 mL (0.5 cup) nondiet soda
Fruit	118 mL (0.5 cup) fat-free milk
	1 small apple
	1 small orange
	One half banana
Snack	118 mL (0.5 cup) applesauce
	6 to 8 hard candies
	One half bag Skittles
	One half roll Life Savers
	15 mL (1 tbsp) honey
	15 mL (1 tbsp) jam/jelly
	15 mL (1 tbsp) sugar in water

anesthesia-trained dentist, emergency medical services (911) should be activated immediately in the ambulatory office setting.

TREATMENT OF HYPERGLYCEMIA

If the diabetic patient presents for surgery and sedation/general anesthesia with a significantly elevated blood glucose level, the dentist must determine if the patient is a good candidate for treatment that day or if better glycemic control should be established via physician consultation or intervention. There is controversy surrounding the specific cutoff for blood glucose levels in which dental or oral surgery treatment should not take place. As stated previously in part 1 of this series, SAMBA generally recommends that a blood glucose level less than 180 mg/dL (10.0 mmol/L) is optimal for the ambulatory office setting.²² Because of changes in hypoglycemic regimens and the stress of anesthesia/surgery, somewhat higher blood glucose levels are likely acceptable. Although blood glucose levels can likely be managed intraoperatively, the sedation/general anesthesia provider should also be concerned with a potential for compromised wound healing and postoperative glycemic stability. Ideally, a collaborative decision to render or withhold treatment should be made with the dentist or surgeon.

According to SAMBA, intraoperative hyperglycemia can be treated by “the rule of 1800” for rapid-acting insulin or “the rule of 1500” for regular insulin.²² Prior to surgery, the patient’s daily insulin requirement should be determined. The total daily insulin requirement can be divided into 1800 or 1500 (for rapid-acting vs regular insulin respectively) to find the expected reduction in blood glucose per unit of insulin. For example, if a patient uses the rapid-acting insulin, lispro, along with the long-acting insulin, glargine, and has a daily insulin requirement of 60 units, then 1 unit of lispro, aspart, or glulisine insulin will reduce that patient’s blood glucose by approximately 30 mg/dL (1.7 mmol/L).

For patients on a sliding-scale insulin regimen, the correction factor indicating how much 1 unit of insulin will drop blood glucose levels is generally known, but can be confirmed with the 1500/1800 rule. Rapid-acting insulin may be given subcutaneously; regular insulin may be administered subcutaneously or intravenously. If insulin is administered intravenously, the anesthesia provider should remember that a portion of the insulin will be lost through binding to the intravenous tubing and that the duration of action of the insulin will be shortened relative to subcutaneous dosing. Insulin, whether supplied by the patient or anesthesia provider, must be available perioperatively for all patients taking rapid-acting or short-acting insulin.

OTHER CONSIDERATIONS

For office-based surgery and anesthesia, the diabetic patient should be treated as the first patient early in the morning. Because postoperative hypoglycemia and hyperglycemia are associated with poor patient outcomes, blood glucose levels must be monitored after surgery and anesthesia are ended.²⁴ Diabetic patients should travel to and from the surgical appointment with easy-to-administer hypoglycemic treatments such as juice or glucose gel/tablets.^{23,32} If the surgical procedure precludes normal postoperative diet (ie, oral surgery), then oral antidiabetic medications should be postponed until normal caloric intake is resumed.²² Patients who are unable to consume calories and have received perioperative insulin administration should be observed on site until the risk of hypoglycemia can be ruled out; this is usually 1.5 hours for rapid-acting insulin and 3–4 hours for regular-acting insulin.²² Regular blood glucose checks are advised after discharge until 1 day postop at a minimum.

Postoperative nausea and vomiting are common in many diabetics; therefore, aggressive measures should be taken to prevent them. Dexamethasone will increase in blood glucose up to 20% above baseline levels.¹⁷ If used, dexamethasone doses should be limited to 4 mg to prevent unwanted perioperative hyperglycemia. Other commonly used antiemetics are not contraindicated. The anesthesia provider should give both oral and written instructions to the patient and his or her immediate caretaker concerning the preoperative and postoperative management of the patient’s diabetes.

SUMMARY

A significant percentage of the patients that present for surgery and anesthesia in the ambulatory setting have type 2 diabetes. It is paramount that all anesthesia providers have a firm grasp on the concepts associated with the pathophysiology of type 2 diabetes and associated disease states that frequently accompany the diabetic patient. It is also of utmost importance that anesthesia providers understand the pharmacokinetics and pharmacodynamics of the many different types of oral and injectable antidiabetic drugs that patients with the disease often utilize. Regimens of the various time-sensitive insulin therapies must also be understood. This second installment of this 2-part series on the anesthetic management of type 2 diabetes has addressed the pharmacology of the various medications used to treat the disorder and has reviewed the most recent guidelines for blood glucose management in ambulatory surgical patients.

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CONTINUING EDUCATION QUESTIONS

This continuing education (CE) program is designed for dentists who desire to advance their understanding of pain and anxiety control in clinical practice. After reading the designated article, the participant should be able to evaluate and utilize the information appropriately in providing patient care.

The American Dental Society of Anesthesiology (ADSA) is accredited by the American Dental Association and Academy of General Dentistry to sponsor CE for dentists and will award CE credit for each article completed. You must answer 3 of the 4 questions correctly to receive credit.

Submit your answers online at www.adsahome.org. Click on “On Demand CE.”

CE questions must be completed within 3 months and prior to the next issue.

1. Biguanides work by all of the following mechanisms EXCEPT:
 - A. Decreasing the amount of glucose absorption in the intestines
 - B. Increasing gluconeogenesis in the liver
 - C. Causing tissues to be more sensitive to the effects of insulin
 - D. Causing peripheral tissues to uptake more glucose
2. If a patient takes lispro and glargine insulin, how should the insulin regimen be adjusted prior to surgery under general anesthesia?
 - A. The lispro should be taken the day before surgery as usual
 - B. The lispro should be held on the day of surgery
 - C. The glargine should be taken at 75–100% of the nighttime dose the day before surgery
 - D. All of the above
3. A patient takes lispro and glargine insulin, and has a daily insulin requirement of 70 units. During general anesthesia, the patient's blood glucose level is measured at 250 mg/dL (13.9 mmol/L). You do not know the patient's correction factor. If you wanted to lower the patient's blood glucose level to approximately 150 mg/dL (8.3 mmol/L), how many units of lispro would you administer subcutaneously according to standard formulas?
 - A. 4
 - B. 3
 - C. 2
 - D. 1
4. During general anesthesia, your 68-kg (150-lb) patient's blood glucose level is measured at 50 mg/dL (2.8 mmol/L). Which of the following would be an acceptable option for treatment of the patient's hypoglycemia?
 - A. An intravenous solution of 50 mL dextrose 50%
 - B. An intravenous solution of 500 mL dextrose 5%
 - C. An intravenous solution of 500 mL lactated Ringer
 - D. Both A and B are acceptable