PHARMACOLOGY FACTS

Perioperative Glycemic Control in Patients With Diabetes

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POOR PERIOPERATIVE OUTCOMES such as diabetic ketoacidosis, impaired wound healing, infection, and mortality have been associated with uncontrolled glucose in the perioperative continuum of care.[1-6] With a prevalence of combined diagnosed and undiagnosed diabetes in the United States of 9.4%, encountering this patient population in the perioperative setting is becoming more routine.[7] Several barriers can obstruct optimal care delivery to these patients, and addressing these barriers is complex because of the multiprofessional perioperative pathway that spans across several phases of care. With increased emphasis on quality of care and improved surgical outcomes, this review aims to provide a deeper understanding of the significance of perioperative management of patients with diabetes.

Type 1 diabetes affects approximately 5% of the US population and accounts for 5% to 10% of all diabetes diagnoses.[8] The pathophysiology of type 1 diabetes is related to the development of one or more autoantibodies that cause pancreatic β-cell destruction. The rate of β-cell destruction is variable and can occur rapidly over a few weeks or slowly over years. Patients with type 1 diabetes ultimately become dependent on exogenous insulin for survival. Without insulin supplementation, even for short periods, the risk of developing life-threatening ketoacidosis increases.

Type 2 diabetes is by far the most prevalent form of diabetes in the United States and accounts for 90% to 95% of diagnoses.[8] The pathway of pancreatic β-cell demise and dysfunction in type 2 diabetes is not fully understood. Intricately involved, however, is insulin resistance followed by deficient β-cell insulin secretion. Insulin secretory defects appear to be related to inflammation, metabolic stress, and genetic factors as opposed to autoantibody-mediated β-cell destruction as in type 1 diabetes. The disease mechanism of insulin resistance, rather than absolute insulin deficiency, typically makes insulin supplementation unnecessary in individuals with type 2 diabetes. Most individuals are maintained on oral antidiabetic agents, but some may progress to requiring insulin supplementation.

Insulin is the most important hormone involved in glycemic control. Its primary mechanism of action is to reduce circulating glucose concentrations within the body by increasing uptake of glucose into peripheral tissues and decreasing endogenous glucose production. Beyond the well-known effects on glucose metabolism, insulin has other properties that are beneficial to the surgical patient. Insulin leads to the reduction in several proinflammatory mediators, such as interleukin-1β, interleukin-6, and tumor necrosis factor-α. In addition, antithrombotic, antifibrinolytic, and antioxidant properties have been described.[9]

Inadequate availability of insulin results in low intracellular glucose levels and subsequent reliance on alternative energy sources. Lipolysis, or the breakdown of fat, becomes an alternate means of providing metabolic energy. Acidic byproducts of lipolysis, known as ketone bodies, can accumulate and cause a metabolic derangement known as ketoacidosis. Diabetic ketoacidosis tends to occur in patients with type 1 diabetes, who produce little or no insulin. Often individuals with type 2 diabetes produce enough insulin to prevent the development of ketoacidosis.[8]

Glucose homeostasis is disrupted in the perioperative environment. Transient insulin resistance

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manifests itself through several complex and poorly understood mechanisms.[9,10] In addition, insulin secretion is inhibited by catecholamines released during surgical stress. Other contributing factors include intracellular potassium depletion, vasopressors, inhaled anesthetics, and intravenous (IV) anesthetics such a propofol and opioids.[9] An often underestimated cause of perioperative hyperglycemia is dexamethasone. Because of the drug-disease interaction, dexamethasone should not be used in patients with diabetes. In instances where there are no other acceptable alternatives, the lowest effective dose should be administered, and postoperative hyperglycemia should be anticipated.

Hyperglycemia during the perioperative period can have a negative impact on postoperative outcomes. Acute hyperglycemia suppresses immune function, increases circulating inflammatory cytokines, and impairs the ability of the host to combat infection.[11,12] Perioperative development of acute hyperglycemia has been associated with an increased risk for surgical site infections.[1,13] This risk is even more pronounced in patients with diabetes.[6,14] As such, implementation of patient care pathways targeting glucose control during the perioperative phases of care is necessary to optimize surgical outcomes. Also necessary is the need to close the knowledge gap of all perioperative clinicians as it relates to understanding the diabetes disease state and the associated treatment options common in the perioperative environment.

Foundational knowledge of insulin formulations currently on the market is an essential component to perioperative management of patients with diabetes. These formulations differ in onset, peak, mechanism and duration of action, concentration, and route of administration (Table 1).[15] Insulin has historically been categorized into four main types: (1) rapid and short acting, (2) intermediate acting, (3) long acting, and (4) combination (combines a short-acting and an intermediate-acting or long-acting insulin in one formulation). This simple categorization is becoming more complex because of slight but significant nuances in formulations and advances in pharmacologic treatment options. More recent additions to the armamentarium of insulin products include a rapid-acting inhaled insulin; a very long-acting insulin known as insulin degludec; and formulations comprising a long-acting insulin combined with a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 receptor agonists increase glucose-dependent insulin secretion, decrease glucagon secretion, and slow gastric emptying. Formulations with GLP-1 receptor agonists are only approved for use in patients with type 2 diabetes because of their mechanism of action.

Preoperative Assessment and Planning

The criticality of assessing the patient's antidiabetic regimen in the clinic preoperatively is often under-recognized. Preoperative guidance should be provided to the patient both verbally and written on how to appropriately adjust their regimen the day before and the day of surgery to avoid hypoglycemia during the fasting state or hyperglycemia related to omitted dose(s) (Table 2). Adjustments will depend on historical glycemic control (eg, hemoglobin A1c), recent incidence of hyperglycemia or hypoglycemia, surgery-specific preoperative dietary recommendations, type of surgery/procedure to be performed, and the patient's home antidiabetic regimen.

Intermediate-acting and long-acting insulin formulations are considered basal insulin and when dosed properly keep blood glucose at a consistent level during periods of fasting. Basal insulin is usually taken once or twice daily, depending on the insulin formulation. Rapid-acting and short-acting insulin is used to emulate pancreatic insulin secretion and administered at meal time. It is also used to correct the presence of hyperglycemia after it develops. This regimen, as described previously, is a basal-bolus insulin regimen. Consideration should be given to reduce the dose of intermediate-acting and long-acting insulin the night before surgery and the morning of surgery. Doses of rapid-acting and short-acting insulin should be administered normally on the day before surgery but should be held on the day of surgery unless it is needed to correct hyperglycemia. Combination formulations that comprise rapid-acting or short-acting insulin should also be held on the day of surgery. Alternative therapy such as 50% of the patient's typical dose using an intermediate-acting insulin should be administered instead. Insulin pumps (filled with rapid-acting or short-acting insulin) should be programmed to a sleep or sick day setting as dictated by the patient's