

MODERN STRATEGIES FOR THE ANESTHETIC MANAGEMENT OF THE PATIENT WITH DIABETES

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Summary

Diabetes Mellitus (DM) is an endocrine disease with high incidence. Long-term complications involve the eyes, kidneys, nerves, and blood vessels, resulting in hypertension, cardiac ischemia, atherosclerosis, and renal failure, among other syndromes. Given this prevalence, anesthesiologists, especially those who work with older patients, may expect to encounter some aspect of diabetes almost every day. Appropriate preoperative evaluation and rational intraoperative and postoperative management of this complex disease in elective and emergency circumstances are essential. Recent studies have emphasized the need to maintain tight perioperative glycemic control and new guidelines have been presented.

Epidemiology/Incidence

In the United States, approximately 20.8 million people (7% of the total population) suffer from diabetes mellitus. Currently, type 2 diabetes represents 90-95% of all cases, leaving type 1 diabetes to account for the remaining 5-10%¹. Approximately one third of diabetic patients are presently unaware of their pathology and therefore do not seek care. Up to half of all newly identified cases of renal failure are related to diabetes mellitus. Those with diabetes have a significant chance of also suffering from other co-morbidities, including stroke and coronary artery disease (CAD). Diabetes is the 7th leading cause of death¹. As well, compared to the non diabetic population, diabetic patients have an increased rate of hospitalization frequency, longer hospital stays, and a greater number of ambulatory care visits².

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Glucose Physiology

Glucose is a crucial fuel source, and insulin facilitates glucose movement into cells in a process that also requires potassium and phosphate. Red blood cells, healing wounds, the brain, and the adrenal medulla require glucose for fuel, totaling approximately 2 mg/kg/min. When controlling blood glucose, close monitoring is crucial. Reagent strips containing glucose oxidase, used in conjunction with glucometers, provide rapid and reliable results. It is imperative to know the insulin regimen or oral hypoglycemic agent of each patient and then measure the blood glucose preoperatively, intraoperatively, and postoperatively. The degree of end-organ damage, coronary artery disease, and autonomic neuropathy can contribute to the risk of aspiration, myocardial infarction, and peripheral neuropathy.

Hyperglycemia

Hyperglycemia (>120 to 200 mg/dL) is most often caused by insulin deficiency, insulin receptor resistance, or glucose overadministration. Hyperglycemia produces osmotic diuresis; exacerbation of brain, spinal cord, and renal damage by ischemia; delayed gastric emptying; hypophosphatemia; delayed wound healing; and impaired white blood cell function. Maternal hyperglycemia increases the risk of neonatal jaundice, the risk of neonatal brain damage, and fetal acidosis if the fetus becomes hypoxic.

Even with supramaximal levels of insulin, adults can only use glucose at a rate of 3 to 5 mg/kg/min at rest (approximately 240 mL/hour of 5% solutions). The maximal rate of metabolism is less in stress states and more with increased metabolic rates. In general, the rate of administration should be limited to 2 to 3 mg/kg/min (120 to 180 mg/kg/hour), which is 100 g/hour for a 70-kg person (200 mL of a 5% dextrose solution/hour). Healthy infants and children become hyperglycemic if 5% dextrose is included in maintenance fluids. The maximal rate of glucose disposition in young children is 4 to 8 mg/kg/min, and the optimal rate is less than 5 mg/kg/min. In reviewing the literature, it is not clear if glucose administration is necessary for intraoperative management of most patients.

Pathology

Hyperglycemia of diabetes is the consequence of relative or absolute deficiency of insulin and a relative or absolute excess of glucagon. In type 1 diabetes, there is an absolute deficiency in insulin production, and without insulin, patients die. These patients eventually become dependent on exogenous insulin to prevent lipolysis and eventually ketoacidosis. The onset of type 1 diabetes usually occurs by adolescence, although it may occur at any age and is thought to result from autoimmune destruction of islet cells in the pancreas.

Type 2 diabetes is characterized by a relative deficiency in insulin, typically caused by insulin resistance. The onset of this type of diabetes is usually in adulthood, although there is a trend of decreasing age of onset of type 2 diabetes. Type 2 diabetes almost certainly has a heterogeneous group of etiologic factors. However, commonly associated findings in type 2 diabetes are obesity, abnormal insulin levels, and a strong genetic component.

A third type of diabetes mellitus is gestational diabetes. Gestational diabetes is defined as any degree of glucose intolerance with the onset first recognized during pregnancy. Gestational diabetes complicates approximately 4% of all pregnancies in the United States, which results in about 135,000 cases annually. Clinical recognition of gestational diabetes is important because therapy and antepartum fetal monitoring can reduce perinatal morbidity and mortality. Maternal complications related to gestational diabetes include an increased rate of cesarean delivery.

During the past decade, a new disorder known as syndrome X has been described. As the name implies, it is a syndrome rather than a specific disease state. The hallmark of syndrome X is insulin resistance with hyperinsulinemia. The underlying pathology is similar to type 2 diabetes; however, syndrome X patients do not exhibit hyperglycemia. Syndrome X patients may never develop type 2 diabetes. The clinical significance of this condition stems from its association with multiple metabolic abnormalities, including low levels of high-density lipoprotein (HDL), increased blood pressure, and increased plasminogen activator inhibitor-1 levels. All these abnormalities have definite or possible association with coronary artery disease. Whether syndrome X and type 2 diabetes are on a spectrum of disease with insulin

resistance as a common denominator or are totally separate entities has yet to be clarified.

Anesthetic Considerations

Pre-Operative

The preoperative physical examination and history may reveal extensive diabetic neuropathy, which may be seen as orthostatic hypotension, syncopal episodes, mononeuropathies or polyneuropathies, and erectile or bladder dysfunction. Patients may present with a number of additional findings, including cerebrovascular disease, renal dysfunction, microalbuminemia, and tight, waxy skin. In an estimated 30% to 40% of diabetic patients, glycosylation of the atlanto-occipital joint may limit joint mobility and cause difficulty with airway management (i.e., stiff-neck syndrome)⁴. Laboratory evaluation of hemoglobin A_{1c} is an accurate measure of the severity of hyperglycemia and has been shown to correlate directly with increased rates of complications. Conversely, lower hemoglobin A_{1c} values are associated with decreased risk and can be considered a measure of the quality of the diabetic care or lack of presence of the disease itself. Hemoglobin A_{1c} provides the best evidence of overall blood glucose control over the past 1 to 2 months and is replacing the oral glucose tolerance test as the gold standard for diagnosing diabetes and for level of control of the disease⁵. A Hemoglobin A_{1c} of $\leq 7\%$ is considered to be indicative of appropriate glycemic control and can be followed on oral hypoglycemic agents or insulin preparations. Basic electrolyte and renal function tests should be evaluated, especially if the patient has frequent urinary tract infections or renal impairment⁶.

The regimen selected to manage diabetics undergoing surgery has become standardized in most facilities in recent years, with a target glucose and maintenance in the range of 80-110 mg/dl. Frequent glucose monitoring and preparation for insulin administration are essential for the diabetic patient and this includes a preoperative level, routine intraoperative levels, and postoperative assessment. Short-acting insulin morning doses are usually held in as much as the patient will be NPO and not eating breakfast the morning of surgery. Intermediate and longer acting insulin preparations are typically continued. Shorter

acting insulin is administered to target the 80-110 mg/dl range. Most protocols are based on an average response for each unit of short acting insulin to lower blood glucose levels by approximately 25 mg/dl.

Perioperative

Because diabetes affects multiple organ systems, the perioperative impact can be profound. Several clinically relevant issues should be considered during perioperative anesthetic management:

1. Diabetes affects oxygen transport by causing glucose to covalently bind to the hemoglobin molecule, decreasing oxygen saturation and red blood cell oxygen transport in diabetic patients⁸.
2. A common complication of diabetes is autonomic dysfunction. Patients in whom diabetes has been poorly controlled for many years often have damage to the autonomic nervous system. One study⁹ demonstrated that diabetic patients with previously diagnosed autonomic dysfunction are at increased risk for intraoperative hypothermia. The pathogenesis may be related to inappropriate regulation of peripheral vasoconstriction to conserve body heat.
3. Autonomic dysfunction also affects the body's ability to regulate blood pressure, leading to significant orthostatic hypotension. This underlying defect is caused by a lack of appropriate vasoconstriction. Denervation may also involve vagal control of the heart rate. The changes in heart rate seen with atropine and β -blockers are blunted in patients with significant autonomic dysfunction¹⁰.
4. Damage to the autonomic nervous system can affect the choice of anesthetic technique. Patients are at significantly increased risk of hypotension caused by induction agents such as thiopental or propofol. Therefore, because of its considerably lower incidence of cardiovascular side effects, etomidate or a reduced dose of propofol are the two most common induction agents for this population of patients.
5. Diabetes has well-defined adverse effects on the cardiovascular system. Men who suffer from diabetes have twice the age-adjusted risk for

coronary artery disease. The risk for women is tripled, indicating that they may be even more sensitive to the cardiovascular effects of diabetes¹¹. Data show that patients with diabetes may be at even greater risk for coronary artery disease than was previously suspected. One study revealed that patients with type 2 diabetes had as great a risk for myocardial infarction as nondiabetic patients who already had a previous myocardial infarction¹². This information reinforces the point that diabetic patients must be carefully evaluated preoperatively for coronary artery disease. It must also be remembered that diabetic patients are more likely to have silent ischemia. They may not experience the classic chest pain and tightness associated with ischemic heart disease. Questions regarding exercise tolerance and shortness of breath with exertion may provide important information regarding underlying heart disease or the degree of compensation.

- Diabetes affects the gastrointestinal tract in several ways. First, it damages the ganglion cells of the gastrointestinal tract, inhibiting motility, delaying gastric emptying and overall transit time through the gut. Theoretically, all diabetic patients have delayed gastric emptying and many practices treat these patients with the same considerations as patients with full stomachs. Thus, preoperative treatment with agents that inhibit acid secretion, neutralize stomach acid, and increase gastric emptying (e.g. famotidine, bicitra, and metoclopramide) is essential. Rapid-sequence induction is commonly employed to try to minimize the risk of aspiration.

Peri- and intraoperative

Perioperative and intraoperative glycemic-control regimens depend on several factors. Patients with type 1 diabetes are at risk for ketonemia if they are without insulin. The risk of ketosis is amplified when the patient undergoes the stress of surgery. Second, the degree to which blood sugar levels are chronically controlled affects management. The amount of exogenous insulin a patient normally requires is important in deciding how blood glucose should be treated intraoperatively. The magnitude of the surgery plays an important role in determining therapy. There are few prospective studies comparing regimens, even though there are many

different protocols for preoperative and intraoperative insulin management. Some of the more common protocols are discussed.

Sliding Scale:

The typical “sliding scale” is destined to fail because it involves the administration of a fixed dose after documentation of hyperglycemia. A revised protocol has been used in our department at LSU School of Medicine in New Orleans successfully to manage hyperglycemia and provides excellent glucose control throughout the perioperative period [**Fig. 1: Insulin protocol**].

Figure/Chart 1

Insulin Infusion Protocol Intravenous Insulin Infusion for Adults

- Discontinue all previous diabetes medications including SQ insulins.
- Mix Infusion: Human Regular Insulin 100 units in 100 ml NS (1 Unit/ml)
- Check Potassium: if less than 3.5 mEq/L, call MD before starting infusion.
- Initiate Insulin infusion:
Algorithm 1: Start with most patients
Algorithm 2: Patients with post coronary bypass surgery, or solid organ transplantation, or receiving glucocorticoid therapy, or diabetes receiving more than 80 units of insulin/day.

Patient Age	Weight kg		
Blood glucose level (mg/dl)	Initial Insulin Infusion rate Units/hour		
	Algorithm 1	Algorithm 2	Other
Less than 60	<i>Call Anesthesiologist</i>		
61-109	<i>Hold insulin infusion, check glucose in 1 hour and follow the schedule</i>		
110-119	0.5	1	_____
120-149	1	1.5	_____
150-179	1.5	2	_____
180-209	2	3	_____
210-239	2	4	_____
240-269	3	5	_____
270-299	3	6	_____
300-329	4	7	_____
330-359	4	8	_____
360-399	6	10	_____
400 or Greater	8	12	_____

- Monitoring:
 - Check Glucose every 1 hour until 3 consecutive levels to reach the Goal of 80-110 mg/dl range; Follow the titration schedule if the goal is not achieved
 - When the levels are in desired range 80-110 mg/dl; decrease the check of Blood Glucose every 2 hours x 4 hours then every 4 hours.
 - Restart the process at 5a every 1 hour if there is a change in the infusion rate.
(Modified from the Ochsner Medical Center in Kenner, Louisiana)

*Table 1
Krinsley Protocol*

Diet	Monitoring
NPO	Q6 hours. 6AM, Noon, 6PM, Midnight
PO Diet	1 Hour Before Meals. QHS
Tube Feedings	Q6 hours. 6AM, Noon, 6PM, Midnight

Glucose Value	Action (SubQ insulin)
<140	No Treatment
140-169	3 units Regular Insulin
170-199	4 units Regular insulin; Recheck glucose value in 3 hours
200-249	6 units Regular insulin; Recheck glucose value in 3 hours
250-299	8 units Regular insulin; Recheck glucose value in 3 hours
300 +	10 units Regular insulin; Recheck glucose value in 3 hours

On the day of surgery, severe diabetic patients receive a dextrose infusion (2 mg/kg/min) and it is started at the time a meal would have been ingested, and glucose is measured preoperatively. For patients currently receiving insulin, an insulin infusion (0.25 units/mL) is started at a rate of 0.5 to 1.25 units/hour, depending on the amount of insulin normally administered and the current glucose level. Blood glucose is monitored hourly, and the infusion rate is adjusted to maintain glucose at 80 to 110 mg/dl. Once the blood glucose level is stable, urine glucose levels and ketone bodies can be checked to ensure that glycosuria due to a low threshold does not confuse interpretation of urine.

For patients requiring more than 50 units/day, which is an indication that the diabetes is poorly controlled, or for the insulin-treated diabetic undergoing major surgery, a more intense monitoring and treatment regimen has been described. Long- and intermediate-acting insulin is discontinued, and the patient is managed with an intravenous insulin infusion or scheduled subcutaneous insulin perioperatively. Twelve hours before anesthesia oral intake must be stopped because significant gastroparesis exists in these patients. Patients are administered a histamine (H₂) blocker along with the gastric-emptying drug metoclopramide the night before and the morning of surgery. This management is quite challenging and time consuming for the healthcare team.

When oral intake stops, maintenance fluids containing dextrose at 2 mg/kg/min are started and should be continued throughout the procedure. Glucose is measured before induction and hourly until stable postoperatively. Urinary ketones are measured every 6 hours. An insulin infusion is started with an initial rate of 1 to 2 units/hour or to match the amount administered hourly the previous day if good control was achieved. Higher doses are required for patients with obesity, liver disease, steroid therapy, or severe infection. Extremely high rates (≥ 80 units/hour) may be required during stressful procedures (e.g., cardiopulmonary bypass)¹³. The frequency of glucose measurement can be decreased once the glucose level has remained stable and within the desired range for 3 hours.

Provided a patient has reasonable glucose control (≤ 130 mg/dL), an alternative to an infusion would be to hold all short-acting insulin and give one half of the intermediate- or long-acting insulin the morning of the surgery. It is imperative to provide close perioperative glucose and electrolyte monitoring. Though poorly controlled glucose postoperatively is a cause of adverse outcomes, there is no clear consensus about the specific method of insulin therapy or the exact range of blood glucose which can affect morbidity or mortality¹⁴. Cerebrovascular accidents, peripheral vascular disease, and cardiovascular infarction are commonly encountered in diabetic patients. The diabetic patient typically has accelerated atherosclerosis related to their disease process and therefore, through preoperative assessment is essential.

Strategies designed to reduce the risk of labile blood pressures and myocardial ischemia related to autonomic or vascular disease may include: β -blockade to blunt the stress of induction, a narcotic-based anesthetic to minimize cardiopulmonary depression, and prophylactic nitroglycerin in these patients with their significant risk of coronary artery disease. Commonly associated conditions include obesity and stiff cervical joints, which may make airway management challenging. Associated cardiovascular conditions often result in the need for additional invasive monitoring.

Multiple protocols have been published utilizing chemistry-based analyzers among cardiovascular surgery patients, with targeted blood glucose ranges of

72-144 mg/dl, 100-139 mg/l, or 100-200 mg/dl without clinically significant hypoglycemia¹⁵ (Table 1).

Postoperative

There are a few oral medications that should be reinstated with caution. Generally the preoperative diabetes treatment regimen (oral or oral plus insulin) may be reinstated once the patient is eating well. However, there are a few caveats for certain oral hypoglycemic agents. Metformin should not be restarted in patients with renal insufficiency, significant hepatic impairment, or congestive heart failure. Sulfonylureas stimulate insulin secretion and may cause hypoglycemia; they should be started only after eating has been well established and serum glucose levels have been checked and are in the appropriate range. A step-up approach can be used for patients on high dose sulfonylureas, starting at low doses and adjusting them until the usual dose is reached.

As discussed earlier, insulin infusions should be continued in patients who do not resume eating postoperatively. Maintaining a tight glucose control (<110 mg/dL) improves patient outcomes in patients in the ICU or OR¹⁶. However it must be noted that there can be a significant financial burden on the hospital to effectively carry out tight glucose control on multiple patients simultaneously. Once it seems likely that solid food will be tolerated, the insulin infusion can be discontinued 15 to 30 minutes prior to eating, and the patient given subcutaneous insulin at that time.

Patients who were taking subcutaneous insulin in the early postoperative phase, before alimentation is restarted, should continue this treatment along with intravenous dextrose (5 to 10 gm of glucose/hr = 100 to 200 mL/hr of D5W solution) to prevent hypoglycemia.

Complications

Acute Hyperglycemia

The cellular effects of acute hyperglycemia are poorly understood, but reports have begun to shed some light on alterations in normal cell functions at the molecular level. One study¹⁷ showed that acutely elevated glucose levels depress endothelin-induced calcium signaling in rat mesangial cells, thereby

depressing the contractile state of glomerular cells. Such information supports the hypothesis that acute hyperglycemia can affect cellular functions and may lead to clinically evident pathology.

Acute consequences of elevated serum glucose levels include impaired wound healing, dehydration, impaired immune system response, and proteolysis. Osmotic diuretic effect of high serum glucose levels are due to the dehydration seen during acute hyperglycemia. Patients with diabetes are well known for having poor wound healing, which is commonly believed to be caused by impaired blood flow to the wound. However, there is evidence that acute hyperglycemia may impair fibroblast activity and impair vitamin C uptake by cells, thereby inhibiting new collagen synthesis¹⁸.

In addition to delayed wound healing, elevated glucose levels also inhibit immune function, and increase the risk of postoperative infection. One study¹⁹ suggests that continuous insulin infusions, used to control intraoperative and postoperative glucose levels, decrease the incidence of sternal wound infections after cardiac surgery. A second study²⁰ found that aggressive glucose control intraoperatively significantly increased neutrophil activity in vitro. Alveolar macrophages from normal hosts demonstrate impaired respiratory burst when exposed in vitro to elevated glucose concentrations²¹. Taken together, these data indicate that tight glucose control intraoperatively may significantly influence the ability of patients to recover more quickly from surgery.

Long term complications of diabetes can be classified into macrovascular and microvascular disease. Manifestations from these two separate pathological pathways usually co-exist in the affected patient. Macrovascular disease, which affects the large vessels of the body, such as the coronary or lower extremity arteries (e.g., femoral, popliteal), may result in myocardial infarction and peripheral vascular occlusive disease, respectively. Up to 80% of deaths in people with type 2 diabetes are attributed to cardiovascular disease and stroke²². The increased prevalence of macrovascular disease in people with diabetes is due to many factors including, but not limited to, obesity, lipid abnormalities, hypertension, hyperglycemia, hypercoagulation, platelet dysfunction, inflammation, and endothelial dysfunction^{23,24}.

Diabetic microvascular disease affects the small vessels, such as those supplying the retina, nerves, and kidneys. End organ damage can lead to diabetic retinopathy and blindness, diabetic neuropathy, which may result in lower limb amputation, and diabetic nephropathy, often leading to end-stage renal disease requiring dialysis or transplantation. It is well established that chronic hyperglycemia results in these primary chronic microvascular complications of diabetes²⁵. Diabetes is the leading cause of renal failure and adult blindness in developed countries, contributing to >43,000 new cases²⁵ of end-stage renal disease and 24,000 new cases of vision loss each year in the US.

Neural Problems

There is both clinical and experimental evidence which suggests that hyperglycemia lowers the neuronal ischemic threshold. In the hypoxic setting, neural tissue cannot metabolize sugar via an aerobic pathway and consequently the sugars undergo anerobic metabolism. The anaerobic pathway produces lactate which further damages the neural tissue and expands the area of necrosis. A recent study by McGirt demonstrated that hyperglycemic patients not on tight glucose control undergoing carotid endarterectomies had an increased risk of perioperative stroke, myocardial infarction, and death²⁶.

Conversely there have been recent studies suggesting that tight glucose control may not be the magic bullet in improving patient outcomes. A study by DeBrouwere suggested that clinical outcomes of cardiovascular surgery patients were not improved by tight glucose control²⁷. Furthermore a study in 2005 by Butterworth showed that tight glucose control did not improve neurological outcomes in patients undergoing open heart surgery²⁸.

Renal problems

A thickening in the glomerulus is the earliest detectable change in the course of diabetic nephropathy. The glomerular thickening causes podocyte broadening and loss in overall podocyte number²⁹. Microalbuminuria occurs when the kidney allows more albumin to pass through the "filter". It can appear 5 to 10 years before other symptoms and is a fairly accurate

indicator for diabetic disease³⁰. Increasing numbers of glomeruli are destroyed by nodular glomerulosclerosis as diabetic nephropathy progresses. Now the amounts of albumin being excreted in the urine increases, and may be detected by ordinary urinalysis techniques. Kidney biopsy clearly shows diabetic nephropathy at this stage.

Kidney failure provoked by glomerulosclerosis leads to fluid filtration deficits and other disorders of kidney function, hypertension and fluid retention result³¹. Other complications may be arteriosclerosis of the renal artery and proteinuria (nephrotic syndrome)³². Also other symptoms may include: edema (usually around eyes), anorexia, nausea, vomiting, malaise, fatigue, headache, frequent hiccups, generalized itching.

Diabetic Ketoacidosis

Diabetic ketoacidosis is an emergent condition often manifested in the diabetic patient with leukocytosis and an acute surgical abdominal emergency or with nausea, vomiting, lethargy, and signs of hypovolemia. The priorities are to restore intravascular volume (usually rapid intravenous administration of 1 L of saline); administer regular insulin (0.2 unit/kg) followed by an infusion at a rate of 0.1 unit/kg/hour; eliminate the ketonemia; control blood glucose; and correct the underlying problem (e.g., antibiotics for urosepsis or pneumonia). Patients with ketoacidosis are dehydrated as a result of glucosuria; because the dehydration is caused by water and electrolyte loss, colloids are not indicated. If the patient's osmolality is elevated, 0.45% sodium chloride can be administered, and the volume administered should be guided by the hemodynamic response, acid-base status, and urinary output. Urine or blood ketones may be monitored every 2 hours after the blood glucose is within 100 to 200 mg/dL. The rates of glucose and insulin infusions should both be increased if ketones are still present.

Osmotic diuresis promotes loss of sodium, potassium, magnesium, and phosphate. Despite total-body deficiencies, however, their concentrations may be elevated at the time of presentation because of severe water loss. The best treatment for hyperkalemia in these patients is appropriate therapy for the diabetic ketoacidosis. Potassium levels decrease rapidly with appropriate volume replacement and insulin therapy.

After volume expansion has begun most patients require electrolyte replacement. Alternatively, severe hyperglycemia may extract water from the intracellular space and may dilute the electrolyte concentrations. Potassium should not be administered if its initial level is elevated or patient is anuric. As hydration improves and urinary output increases, potassium, magnesium, and phosphorus should be administered and levels monitored frequently. In general, acidosis should not be treated with buffers. As insulin and glucose levels improve, the ketoacidosis is corrected, and the lactic acidosis resulting from poor perfusion responds to intravascular fluid replacement. If the pH approaches 7.15, the bicarbonate ion concentration is less than 10 mEq/L and hypotension fails to respond to intravascular fluid administration, sodium bicarbonate therapy may be required.

Hypoglycemia

Hypoglycemia (≤ 50 mg/dL) is dangerous, because glucose is the sole fuel source for much of the brain and can result from too much insulin delivery. Threshold levels depend on age. Irritability, seizures, tachycardia, hypotension, and respiratory failure are all signs of hypoglycemia. Symptoms commonly occur in adults at blood glucose concentrations below 60 mg/dL or in infants with levels below 30 mg/dL. Symptoms are seen at higher levels in diabetics than in nondiabetics and are generally obscured by general anesthesia since irritability and other central nervous systems related manifestations can not be observed while unconscious and tachycardia along with hypotension can be easily misinterpreted intraoperatively as having a different origin. Neurologic and electroencephalographic depression appears at 50 to 55 mg/dL in nondiabetics and 70 to 85 mg/dL in diabetics³³. There are no studies, as of yet, evaluating glucose levels and brain wave monitor changes in humans.

During labor, maternal starvation-induced ketosis has adverse fetal effects, including fetal ketonemia, hypoxia, and fetal lactic acidosis³⁵. Neonates are at increased risk for hypoglycemia because of limited glycogen stores and from large amounts of fetal insulin production in response to gestational hyperglycemic states. Adults are also at risk for hypoglycemia from inadequate gluconeogenesis coupled with inadequate

nutritional intake or from excess insulin (e.g., from an insulinoma, pancreatic islet cell adenoma, or carcinoma; iatrogenic overadministration). Hypoglycemia can also follow too abrupt cessation of dextrose infusion during total parenteral nutrition (i.e., reactive hyperinsulinemic states). Inadequate gluconeogenesis occurs in liver failure, cortisol deficiency (primary or secondary), inadequate glucagon response, growth hormone deficiency, and during β -adrenergic blockade. Fasting in women is likely to produce hypoglycemia in 24 hours, whereas men tolerate about 72 hours of fasting³⁵. The incidence of hypoglycemia in healthy infants and children is low (2 of 446) with 4 to 8 hours of fasting³⁶. Fetal hypoglycemia occurs if maternal glucose is greater than 150 mg/dL, because glucose crosses the placenta, inducing fetal insulin secretion. Treatment consists of an intravenous bolus of 5 g of dextrose followed by increasing the rate of dextrose infusion by 1 to 2 mg/kg/min.

Neural Tissue Damage

Clinical and experimental evidence suggests that hyperglycemia lowers the neuronal ischemic threshold, potentiates stroke volume in focal ischemia, and is associated with morbidity and mortality in the surgical critical care setting. It remains unknown whether hyperglycemia during carotid endarterectomy (CEA) predisposes patients to perioperative stroke and operative related morbidity and mortality. Independent of previous cardiac disease, diabetes, or other comorbidities, hyperglycemia at the time of CEA was associated with an increased risk of perioperative stroke or transient ischemic attack, myocardial infarction, and death. Strict glucose control should be attempted before surgery to minimize the risk of morbidity and mortality after CEA²⁶.

Treatment options and new guidelines

Glycemic Control

Because of co-morbidities and the high risk of coronary heart disease, which may be relatively asymptomatic compared to the non diabetic population, careful assessment of diabetic patients prior to surgery is essential to maximize the best

possible outcome. Diabetes mellitus is also associated with increased risk of perioperative infection³⁵ and postoperative cardiovascular morbidity and mortality³⁸. Hyperglycemia occurs commonly in critically ill diabetic patients; but also, is frequent in those who have a history of euglycemia/normoglycemia. This is particularly seen in patients who have been placed on steroids over a period of time.

Surgery and general anesthesia can result in a state of relative insulin hyposecretion and insulin resistance³⁹ by release of hormones such as glucocorticoids, growth hormone, catecholamines, and glucagon⁴⁰. The magnitude of counterregulatory hormone release varies per individual and is related to the extent of the surgery and additional postoperative factors such as sepsis. Another factor in perioperative management is the wide variation in nutritional consumption⁴¹.

Many different data sets show that tight glycemic control decreases mortality and morbidity. Tight glycemic control in ICU patients has been shown to result in reduced morbidity from the prevention of acquired kidney problems, accelerated weaning times off the ventilator, and faster discharge from the ICU/hospital.

A prospective randomized trial conducted by Van den Berghe compared traditional insulin therapy (treat >215 mg/dL) to intensive insulin therapy (80-110 mg/dL) and the study showed a significant reduction in morbidity and mortality in intensive care patients significantly reducing in-hospital mortality from 11 to 7 percent in the entire study population^{42,43}. In a subgroup of patients who stayed in the ICU for three or more days, however, the benefit was much more pronounced, reducing mortality from 21 to 14 percent among patients treated for at least three days and from 26 to 17 percent among those treated for at least five days. Severe complications such as sepsis and organ failure were reduced. Similarly, Lazar showed that tight glycemic control in coronary artery bypass graft patients improved perioperative outcomes and was linked to reducing recurrent ischemic events⁴¹. However, intraoperative data regarding glycemic control is limited to two retrospective studies of diabetic patients undergoing cardiac surgery and demonstrate an association between poor intraoperative glycemic control and morbidity and mortality^{2,45}.

Pharmacologic Considerations

Muscle Relaxants

The use of muscle relaxing agents such as succinylcholine may be used safely in patients with renal insufficiency provided they do not have high baseline serum levels of potassium, since typically there is a transient increase as high as 0.5mEq/L. For this reason, it is inadvisable to use succinylcholine in end-stage renal failure patients unless they have been dialyzed within 24 hours. Close monitoring of train-of-four nerve stimulation allows the clinician to accurately assess the degree to which renal impairment may be affecting drug pharmacokinetics. Rocuronium is another option that can be used as a muscle relaxing agent in a patient with renal disease. Rocuronium is primarily metabolized hepatically and therefore should be used with caution in patients with significant hepatic dysfunction.

Barbituates

The action of thiopental, a rapidly acting barbiturate, is terminated by redistribution and is not affected by renal impairment. However, in patients with severe renal dysfunction (glomerular filtration rate [GFR] <10) 75% of the normal dose is recommended because of accumulation of an active metabolite.

Benzodiazepines

All drugs in this group are extensively metabolized in the liver and are not affected by renal impairment.

Opiates

Morphine has one potentially significant consideration in renal insufficiency. One of its metabolites, morphine-6-glucuronide, is cleared by the kidney. This metabolite possesses opiate activity. For this reason, if utilized, the dose of morphine should be reduced to 75% of the standard dose in patients with a GFR of 10 to 50 mL/min, and 50% of the usual dose in patients with GFR under 10 mL/min. Meperidine, like morphine, has an active metabolite, normeperidine. However, unlike the metabolite of morphine, this molecule exerts an excitatory CNS effect. Therefore, if meperidine is used, doses should be decreased by 50% in patients with a GFR of 10 to 50 mL/min, and 75% with a GFR of less than 10 mL/min.

Fentanyl is an attractive choice for patients with renal dysfunction as it is primarily metabolized in the liver. CYP3A4 is the major catalyst involved in fentanyl oxidation to norfentanyl in human liver. Alterations in CYP3A4 levels or activity, as well as the concomitant administration of other therapeutic agents metabolized by this P450 enzyme, could lead to marked perturbations in fentanyl disposition and, hence, analgesic response.

Conclusion

The prevalence of diabetes mellitus worldwide

requires each anesthesia provider to be well versed in the drugs that are available in its treatment as well as to appreciate the potential complications in the perioperative management of these patients. It is certain that over the coming decades newer modalities will exist in the treatment of this very common disease state. As these treatments became available and as there is increasing understanding of the pathophysiology of diabetes mellitus, the clinical anesthesia provider must continue to educate themselves to ensure the best outcome for this ever growing segment of our population.

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