Preoperative and intraoperative insulin needs in diabetic patients

JEFFREY A. LYNCH, CRNA, BS
Stockton, California

This article provides a basic review of the origin and action of insulin as well as other hormones that affect the level of blood glucose. The review will impart a basic understanding of the hormone and substrate interactions that change blood glucose concentration. With this knowledge in hand, the need for preoperative and intraoperative insulin administration becomes apparent.

Control of glucose levels in diabetic patients is important to a smooth and uneventful anesthetic and recovery period. Every anesthetist should make an effort to understand those conditions that affect insulin and glucose levels in the body and how to balance the levels. In the event that insulin administration is needed, anesthetists should be familiar with the action of insulin.

A review: The actions of insulin

The islets of Langerhans are one of two types of tissue found in the pancreas. The islets contain two major types of cells that can be stained to reveal the different characteristics. Those cells that show staining characteristics for insulin are the beta cells. They have a different form and structure from the alpha cells, the other major type of cells in the islets. The beta cells are responsible for secretion of insulin and the alpha cells are responsible for the secretion of glucagon.

Insulin is a small protein with a molecular weight of 5808. It is made of two chains of amino acids with three disulfide bridges. Two of these disulfide linkages connect the two amino acid chains. The third disulfide bridge connects two amino acids of cystine that are four amino acids apart in the same chain. Insulin was one of the first proteins in which the amino acid sequence was discovered.

To understand the action of insulin on the concentration of blood glucose, one must understand several points about monosaccharides. Three of the monosaccharides that the body deals with are glucose, fructose and galactose. These monosaccharides have molecular weights of approximately 180 gm and are between 8.4 and 8.6 angstroms in size. With such physical characteristics, these monosaccharides cannot readily diffuse through pores in cell membranes. The maximum molecular weight of particles that can diffuse through cell membrane pores is about 100 gm.

The average pore size in cell membranes is about 8.0 angstroms, too small for these monosaccharides to pass through. The fructose and galactose taken in by the body are converted to glucose in the intestinal epithelial calls and in the liver. This leaves glucose as the circulating monosaccharide from which the cells can obtain energy.

Glucose is used for energy of metabolism and it can be trapped within the cells to provide this energy. However, because it will not pass through
pores in the cell membrane, it must diffuse through the membrane. Unfortunately, it cannot do this at a rate sufficient to provide adequate energy for metabolism. Thus, the cells move glucose across the cell membranes by what is called carrier-mediated or facilitated diffusion.

Facilitated diffusion is similar to simple diffusion in that it depends on the concentration of the substance being moved on either side of the membrane. It differs from active transport, in that it cannot move against a concentration gradient. Facilitated diffusion thus moves substances only from a higher to a lower concentration. Glucose combines with the carrier and becomes more lipid soluble. Then, in combination, the carrier and the glucose can diffuse across the membrane, or the carrier can rotate, perhaps like a turnstile, and release glucose on the inside of the membrane. The carrier is then free to diffuse to the other side of the membrane or simply to rotate to the other side of the membrane.

This carrier must be able to combine reversibly with glucose. A protein has been found in cell membranes that is able to combine reversibly with glucose. At present little is known about it, but this protein may be the carrier that moves glucose.

There are a few exceptions, but by and large even with the aid of facilitated diffusion, not enough glucose can enter the cells to provide sufficient energy for metabolism. The most important basic effect of insulin is to increase the rate of glucose transport by seven to 10 times the rate resulting from facilitated diffusion alone. The mechanism for this increase is not completely understood. Whether insulin increases the number of carriers present in the cell membranes or acts to speed the chemical process that controls the attachment and release of glucose to and from the carrier protein is not known.

The aforementioned exceptions to the action of insulin are the red blood cells and the cells in the brain, renal tubular epithelium, and intestinal epithelium. These tissues make up only 5% of the total body weight. (The brain receives glucose by simple diffusion across the blood brain barrier). The remaining 95% of body tissue is at least insulin-sensitive and glucose transportation is enhanced in this manner. Insulin is extremely effective in skeletal muscle cells and adipose tissue cells. Insulin is also effective in the liver, although its effects are different; in the liver, insulin does not enhance glucose transport across hepatic cell membranes but does have anabolic and antitcatabolic effects.

The stimulation of insulin secretion is due to several factors. The major stimulus is the blood glucose level. Amino acids, especially alanine, greatly enhance the stimulatory effect of glucose if both are present simultaneously, but they stimulate the secretion of insulin to a lesser extent in the absence of glucose. Three gastrointestinal hormones that can cause an increase in the secretion of insulin are gastrin, secretin, and cholecystokinin.

The effects of insulin secretion on the liver, skeletal muscle cells, and fat cells are both anabolic and antitcatabolic. In the liver there are two anabolic effects: increased glycogen synthesis and increased fatty acid synthesis. Glycogen synthesis and deposition takes place when insulin stimulates an increase in glucokinase, which increases the amount of glucose phosphorylated and therefore trapped in the liver cells. In the presence of excess glucose, an increase of glycogen synthetase leads to glycogen storage and an inhibition of glycolytic enzymes. This process continues until glycogen stores become sufficient, at which time the mass of the glycogen offers negative feedback to limit further production.

The second anabolic effect consists of (1) an increase in fatty acid synthesis, due to the increase in insulin and glucose which results in an increase in acetyl Co-A carboxylase, the enzyme responsible for the start of lipogenesis. The large amount of alpha glycerophosphate provides the glycerol backbone for triglycerides.

The antitcatabolic effects in the liver are: (1) decreased glycogenolysis by inactivation of phosphorlyase; (2) decreased gluconeogenesis by prevention of the release of amino acids from muscle; and (3) decreased ketogenesis by limitation of conversion of free fatty acids to ketones and facilitation of uptake of beta-hydroxybutyric acid and acetacetic acid (ketocids) by muscles.

In the muscle cells, the anabolic effects of insulin are increased amino acid uptake, increased protein synthesis and increased glycogen synthesis. The antitcatabolic effects are decreased protein catabolism and decreased amino acid output. In fat cells, the anabolic effects of insulin are increased glycerol synthesis and increased fatty acid synthesis by its enhancement of the action of the enzyme lipoprotein lipase. The antitcatabolic effect of insulin is decreased lipolysis. This is due to the
restraining effect on the activity of tissue lipase which is responsible for the breakdown of triglycerides stored in fat cells.  

Hyperglycemia is only one of several results of insulin deficiency. The absence of insulin in the liver causes increased phosphorylase activity, which in turn causes glycogenolysis. There is also an increase in gluconeogenesis from amino acids released from muscles no longer inhibited from amino acid output. Free fatty acids released from fat cells at an accelerated rate (due to lack of restraint on tissue lipase) enter the glucose-free fatty acid cycle.  

This cycle leads to decreased glycolysis, and therefore an increase in glucose-6-phosphate, which in turn inhibits glucokinase, causing a decrease in phosphorylation. This allows glucose to diffuse out of the cell and causes an enhancement of the insulin deficiency on cellular uptake and utilization of glucose. The net effect is a constantly increasing blood glucose concentration. In addition to hyperglycemia, there is an accumulation of triglycerides as the activity of lipoprotein lipase falls off. An accumulation of free fatty acids (caused by unrestrained tissue lipase) and buildup of ketones as free fatty acids are oxidized, also accompanies the hyperglycemia. This is all compounded by the release of hormones that tend to increase blood glucose concentration.  

Hormones affecting blood glucose  

Hormones which increase blood glucose are somatotrophin (growth hormone), epinephrine, glucocorticoids, and glucagon. Growth hormone increases both the rate of protein synthesis and the mobilization of fats to provide energy. The amount of protein used for gluconeogenesis and the rate of carbohydrate utilization are decreased by growth hormone. The decrease in utilization of glucose leads to an increase in glycogen storage to the physiologic limits of the cells. At this point glucose uptake decreases, causing a rise in blood glucose. Growth hormone is secreted during hypoglycemia, exercise, trauma or excitement and is dependent on cellular protein and blood glucose levels.  

Cortisol, a glucocorticoid, increases gluconeogenesis up to ten times the normal rate, decreases glucose utilization, and decreases transport of glucose into cells. The decrease in glucose utilization leads to excess glucose-6-phosphate in the liver. This catalyzes dephosphorylation of glucose, and the glucose diffuses out of the liver, raising the blood glucose. In muscle cells, the increases in glucose-6-phosphate would inhibit glucokinase and decrease phosphorylation. Glucose would then be free to diffuse out of the cells. The situations in which cortisol is secreted are trauma, infection, surgical operations, and injection of sympathomimetic drugs.  

Glucagon, which is secreted by the alpha cells in the islets of Langerhans, has an action that is the opposite of the action of insulin. Glucagon increases glycogenolysis in a cascade of events, leading to an amplified response due to an increasing amount of product at the end of each step of the cascade.  

Glucagon also increases gluconeogenesis, proteolysis in extrahepatic tissues and lipolysis in adipose tissue. When blood glucose falls below the normal range, glucagon is secreted. The body also secretes glucagon during times of stress, exercise, starvation, and lack of insulin. The latter effect arises because of the inability of glucose to enter the alpha cells in adequate amounts, causing a fall in intracellular glucose and stimulating the release of glucagon.  

Epinephrine and, to a slight extent, norepinephrine have glucagon-like effects. Epinephrine and norepinephrine increase glycogenolysis and mobilization of fatty acids. Catecholamines therefore tend to raise blood glucose concentrations.  

These hormones are all released during periods of trauma and stress, causing a rise in blood glucose to varying degrees. Surgery causes stress and trauma that is sufficient to effect the release of these hormones and a rise in blood glucose. This rise in blood glucose is proportional to the level of stress due to surgery. Hyperglycemia, increased glucagon levels and insulin resistance have been found following trauma, and these have been compounded by the synergistic effect of cortisol with glucagon to increase gluconeogenesis.  

Cortisol is also thought to exert an anti-insulin effect by activation of an insulin antagonist. This low plasma insulin concentration in conjunction with catecholamines released during periods of stress causes an efflux of amino acids from muscle cells. This efflux can lead to a build-up of ketone bodies from those branched chain amino acids that are not used as substrates for gluconeogenesis. These events all lead to hyperglycemia and can lead to ketosis. Hyperglycemic hyperosmolar nonketotic coma is also a possibility.  

Complications of insulin  

Hyperglycemic hyperosmolar nonketotic coma is marked by blood glucose concentrations in the range of 700-2000 mg/100 ml. Hyperglycemia leads to glucosuria, dehydration, and the hyperosmolar state associated with coma. Two possible causes
of hyperglycemic hyperosmolar nonketotic coma are excess exogenous glucose administered intravenously and insufficient insulin administered before or during surgery.

One case was reported of a patient being given only 50 gm of glucose and 10 units of regular insulin during surgery and having a blood glucose level of 1,185 mg/100 ml postoperatively. The treatment of this state focuses on rehydration over 48 hours. The fluid deficit should be counteracted by giving one third the deficit in the first eight hours, one third in the next 16 hours and one third in the remaining 24 hours. Alternating bottles of normal and half normal saline should be given. The serum potassium should be monitored and replaced with 20-40 mEq/l of intravenous solution as needed. Insulin can be replaced by injection of 10-20 units every two to four hours or by infusion of 4 to 6 units per hour.

Hyperglycemia can be the cause of other conditions, providing additional incentive to control blood glucose levels. Hyperglycemia causes intracellular dehydration because of the osmotic effect of glucose in extracellular fluid. This can be disastrous in patients whose peripheral circulation is marginal in the normal state.

Hyponatremia can also be a consequence of hyperglycemia as glucose moves water from the intracellular space to the extracellular space, causing a dilution effect. Water and sodium loss in the urine can further deplete body sodium. Hyponatremia is manifested by confusion, weakness, apathy, and cramps.

Loss of potassium is also possible. As the sodium level falls, aldosterone works on the distal renal tubules in an attempt to save sodium, thereby causing potassium to be excreted in the urine. Hypokalemia is often manifested by weakness, cardiac arrhythmias, and other neuromuscular function impairments.

Another electrolyte lost in urine during hyperglycemia is phosphorus. Results of low phosphorus levels include a reduced level of 2, 3-diphosphoglycerate, which produces a shift to the left of the oxygen dissociation curve. This is especially hazardous in patients with poor tissue oxygenation due to inadequate perfusion. In addition to electrolyte imbalance, hyperglycemia can cause decreased phagocytosis and antimicrobial activity of polymorphonuclear leukocytes, weakening a patient's defenses against infection.

Methods for controlling insulin and glucose levels

The deleterious effects of surgery related to hyperglycemia and the sequelae that can occur in the diabetic patient have pointed out the need for adequate control of blood glucose and insulin concentrations. Many methods proposed for intraoperative control of blood glucose in the diabetic patient can be found in the literature. Rossi believed this can be accomplished by preoperative injection of intermediate insulin in an amount equal to one half the daily dose and then regular insulin supplements if there is a need to rapidly decrease blood glucose to a level at which the intermediate insulin can be more effective.

Taitelman, Reece, and Bessman used a technique of constant intravenous infusion of insulin intraoperatively at a rate of 1-2 units of regular insulin per hour to control blood glucose levels. This technique was modified by Woodruff and Lewis, who used continuous glucose infusion accompanied by variable insulin infusion. A "mini-pump" constant insulin infusion system was used by Barnett and Robinson to control insulin and glucose levels in their patients during surgery. They obtained good results when patients were given 0.5 units of insulin per hour.

There are other methods for controlling blood glucose levels. These range from avoiding intravenous administration of either insulin or glucose to mixing the two in a single intravenous infusion. Some methods call for the administration of glucose during surgery after giving various percentages of the patient's normal daily insulin preoperatively, while other methods call for glucose administration and no insulin. All these methods claim to have associated low mortality rates, making it difficult to choose the best method. The key, however, is the avoidance of hypoglycemia and hyperglycemia by the monitoring of the patient's blood glucose level during surgery.

The artificial beta cell (Biostator™), produced by Miles Laboratories, is a glucose controlled insulin infusion system that provides continuous glucose monitoring with automatic feedback. Work by Schwartz and Horwitz and their collaborators showed the artificial beta cell to be useful in maintaining blood glucose levels at an acceptable range in diabetic patients.

Their work also suggested that cortisol levels play a part in insulin resistance and that suppression of insulin secretion intraoperatively is related to sympathetic nervous system stimulation and catecholamines released during the stress of surgery. Schwartz and Horwitz also pointed out that in normal patients the degree of hyperglycemia was proportional to the rate of glucose infused intraoperatively.
The artificial beta cell has been used for diabetic patients undergoing major surgery and in obstetrics for diabetic patients having either caesarian sections or vaginal births. Although in the cases of most diabetic patients, the advantages of this glucose controlled infusion system over other systems are not overwhelming, in the case of the brittle diabetic this infusion system provides important data for investigations into hormonal response to surgery.

All anesthetists are not likely to use artificial beta cells on all diabetic patients going to surgery, but the problems of hyperglycemia, hypoglycemia, and ketoacidosis still can be avoided. This can be accomplished by monitoring blood glucose levels, providing proper preoperative insulin dosage, and making informed decisions regarding glucose infusion rates intraoperatively.

REFERENCES


AUTHOR

Jeffrey A. Lynch, CRNA, BS, is a graduate of the Minneapolis Veterans Administration Medical Center School of Anesthesia. He received a BS in nurse anesthesia at the University of Minnesota School of Medicine. He currently is a freelance nurse anesthetist in Stockton, California.