Medications Used in Diabetes in Patients Presenting for Anesthesia

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Effective pharmacological treatment regimens for diabetes usually require the use of several medications. This is because the diabetic state is associated with multiple physiological disturbances, one or a combination of which can lead to considerable morbidity and mortality.

Pathophysiology of Diabetes

In type 1 diabetes, there is failure of the pancreatic islet cells to produce insulin, and this must, therefore, be replaced. The physiological disturbances in type 2 diabetes (formerly known as adult onset diabetes) are more complex. Incompletely understood genetic factors lead to a failure of tissues to respond to insulin. This insulin resistance leads to defects in glucose handling—most notably, failure of glucose uptake by tissue such as muscle, global disruption of glucose utilization, and failure to suppress glucose output by the liver. Over a period of decades the problem of insulin resistance is compounded by a dwindling capacity to secrete insulin, and this, in turn, leads to failure of previously effective oral hypoglycemic drugs.

While abnormal glucose homeostasis is the defining feature of diabetes mellitus, it is not the only defect. Insulin resistance is also associated with obesity, dyslipidemia and hypertension. This constellation of problems is known as the "metabolic syndrome." It may precede clinical diabetes by ten to fifteen years. There is abdominal obesity, as identified by a waist circumference of >40 inches in men and >35 inches in women. Serum triglycerides exceed 150 mg/dL; HDL cholesterol is less than 40 mg/dL in men and <50 mg/dL in women. Blood pressure is >135/85 mmHg. The condition is pro-inflammatory, as shown by elevated blood levels of C-reactive protein and plasminogen activator factor.

Clinical Implications of Diabetes

The clinical implications are serious. The third National Health and Nutrition Examination Survey (NHANES III) revealed an overall prevalence of the

metabolic syndrome of 22 percent, with an age-dependent increase, and its presence increases the risk of developing diabetes mellitus 9- to 34-fold. Seven percent of people in the United States are known to have diabetes. The numbers are still increasing, especially in high risk ethnic populations such as Hispanics and native Americans. Already the toll is enormous. The associated microvascular and macrovascular diseases lead to myocardial infarctions, strokes, chronic kidney disease, retinopathy, neuropathy and foot ulcers. In 2002 the direct and indirect expenditures on these complications were estimated at $132 billion U.S.

Fortunately many of the risk factors for both microvascular and macrovascular complications are modifiable, and clinical trials have furnished the outcome data needed to define the goals and targets of diabetes management. These are well summarized in the American Diabetes Association's "Standards of Medical Care in Diabetes." Smoking cessation is probably the most important modifiable risk factor in preventing cardiovascular disease. Aspirin (75-162 mg/day) is recommended for both primary and secondary prevention of cardiovascular disease and stroke.

For most diabetics the recommended blood pressure goal is 130/80 mmHg. For patients with chronic kidney disease or proteinuria, the goal is an even lower blood pressure, 120/75 mmHg. Thiazide diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blocking drugs have been shown to be useful in reducing cardiovascular complications and diabetic nephropathy.

Treatment of hyperlipidemia has proven beneficial in both primary and secondary prevention of cardiovascular disease in diabetics. The target goal for LDL cholesterol is <100 mg/dL. Diabetics over age 40 who have a total cholesterol >135 mg/dL should be started on therapy with an HMG-CoA reductase inhibitor (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin or rosuvastatin). The importance of triglyceride and non-HDL cholesterol (calculated as total cholesterol-HDL cholesterol) are less well defined, but in general patients with triglycerides over 200 mg/dL or HDL <40 mg/dL should be given additional treatment with a fibrate drug such as benofibrate, bezafibrate or gemfibrozil.

Good glycemic control reduces the rates of retinopathy, nephropathy, and neuropathy. Macrovascular disease has been shown to be benefited in both type 1 and type 2 diabetics. The aim is to achieve hemoglobin A1C levels of less than 7 percent. More stringent goals of normalizing the A1C to less than 6 percent are now being considered in individual patients.

Oral Diabetic Medications

Several diabetic oral agents are now available. They can be used to 1) increase insulin secretion, 2) increase insulin action or 3) modify intestinal absorption of food.

Drugs that Increase Insulin Secretion

Insulin release is stimulated by *sulfonylureas* and by *meglitinides*. Sulfonylureas include glyburide (DiaBeta®, Micronase®, Glynase®), glipizide (Glucotrol®), glimepiride (Amaryl®) and chlorpropamide (Diabinese®). The biological effects of the drugs may be greater than suggested by their half-lives. Chlorpropamide is the longest acting (24 to 72 hours); glyburide has a duration of 20 to 24+ hours; glipizide lasts for 14 to 16 hours. Hypoglycemia is the main problem with their use, and in the long term, they can cause weight gain. Chlorpropamide can cause hyponatremia (by increasing the action of vasopressin).

The meglitinide class includes repaglinide (Prandin®) and nateglinide (Starlix®). These drugs are shorter acting and are usually taken with each meal, the object being to achieve better postprandial glycemic control. Nateglinide should be used cautiously in the setting of chronic kidney disease, as accumulation of active metabolites can lead to hypoglycemia.

Drugs that Enhance Insulin Action

Improved insulin action is effected by metformin (Glucophage®, Fortamet®), which is a biguanide, and the *thiazolidinedione* drugs pioglitazone (Actos®) and rosiglitazone (Avandia®).

Metformin's main effect is to *decrease hepatic glucose production* (it is "antihyperglycemic"). An advantage of the drug is that it causes a little weight loss (most antidiabetic agents cause weight gain). It is less likely to cause hypoglycemia, and it produces small improvements in LDL and HDL cholesterol. Its pharmacokinetics are swift. It achieves peak plasma levels in two hours and is rapidly excreted in the urine in 1.5 to 4.9 hours. It is not bound to plasma proteins, nor is it metabolized. Gastrointestinal side effects are the major limitation to its use. Like its more notorious predecessor phenformin, metformin can cause lactic acidosis. This is a very rare occurrence (9 per 100,000 person-years), but caution is advised with chronic kidney disease, liver disease and clinical settings where tissue perfusion could become compromised (type B lactic acidosis). Cimetidine can delay renal excretion. Metformin should be discontinued for 48 hours after the use of intravenous iodinated contrast material.

Medications Used in Diabetes (cont'd)

The TZDs act by *increasing glucose utilization in muscle and liver.* Their mode of action is only incompletely understood. They bind one or more peroxisome proliferator-activated receptors (PPARs). PPAR-gamma is found in adipose tissue, pancreatic beta cells, vascular endothelium and macrophages. PPAR-alpha is found in liver, heart, skeletal muscle and vascular walls. TZDs can be used in combination with insulin, sulfonylureas or metformin. They may be effective in preventing the progression of insulin resistance to diabetes, and they can lower fasting blood glucose concentrations by 40-65 mg/dL. TZDs have numerous beneficial effects on intermediate metabolic markers (such as lowering of triglyceride and C-reactive protein levels), and their potential impact on cardiovascular risk is under study. Rare cases of serious hepatotoxicity have been reported, and therefore, periodic testing of liver function is recommended. Weight gain accompanies their use, and they cause fluid retention, especially when combined with insulin. Peripheral edema occurs in 2 percent to 5 percent of patients, and they are contraindicated in New York Association class III or IV heart failure. The fluid retention can cause mild hemodilution with a lower hemoglobin concentration for a given red cell mass.

Modified Intestinal Glucose Absorption

Drugs which cause a *decrease in intestinal glucose absorption* include the *alpha-glucosidase inhibitors* (miglitol (Glyset®) and acarbose (Precose™)), and the drugs pramlintide (Symlin®) and exenatide (Byetta®). The alpha-glucosidase inhibitors inhibit the digestion of carbohydrates to monosaccharides, thereby delaying the absorption of glucose. Their main benefit is to decrease postprandial glycemic excursions, with mean improvement in postprandial glucose levels of about 60 mg/dL. Their use is limited by the high incidence of gastrointestinal side effects (70 percent of patients experience flatulence).

Pramlintide is an amylin mimetic. Amylin is co-secreted by pancreatic islet cells with insulin. It delays gastric emptying and lowers postprandial glucose levels. It is administered by subcutaneous injection with each meal. Nausea and headache are the main side effects. When given with mealtime insulin, it can precipitate hypoglycemia; therefore, the mealtime insulin dosages should be reduced by 50 percent when first used with this drug.

Exenatide is an incretin-like compound. Incretins, which include gastric inhibitory peptide and glucagon-like polypeptide, are gastrointestinal peptides that stimulate insulin release in a glucose-dependent fashion. They also inhibit glucagon release and they delay gastric emptying. Exenatide lowers fasting glucose levels and promotes weight loss. It is given subcutaneously before meals. The major limiting side effect is nausea, which can occur in up to 50 percent of patients. Its effect on gastric emptying may interfere with the absorption of many drugs.

Perioperative Management of Diabetic Medications

Oral diabetic medications are usually discontinued perioperatively. Patients are advised to hold their medications on the morning of surgery. Metformin does not need to be stopped sooner than this. Baseline glucose levels should be measured preoperatively, as they help stratify patients according to the risk of postoperative wound infections.

Surgery induces a state of worsening insulin resistance and relative insulin hyposecretion. Inadequate insulin in the perioperative period can lead to diabetic ketoacidosis and fluid volume depletion. Insulin sliding scale regimens can be used to prevent this. It is important to avoid hypoglycemia in the 40-50 mg/dL range because it can induce cardiac arrhythmias and cognitive changes after even a few minutes. Since hypoglycemia can be more difficult to identify in a sedated patient, it is necessary to measure blood glucose more frequently.

There are several useful practice points. Diabetic patients are more likely to have cardiovascular disease. Their frequency of hypoglycemia and hyperglycemia can be used as a guide to perioperative insulin requirements. It is better to schedule diabetic patients early in the morning. Many can simply resume their usual diabetic regimen once they are able to eat.

About 50 percent of daily insulin is needed to meet basal requirements. Patients can usually continue on subcutaneous insulin during short or less invasive surgical procedures. The dosage of intermediate-acting insulins such as NPH insulin should be reduced by 30 percent to 50 percent on the morning of surgery. Long-acting insulins should be reduced by 50 percent on the night before surgery. Patients on insulin pumps can usually continue to use the pump at its basal rate.

For long and complex procedures, intravenous insulin is superior to subcutaneous insulin, as there is more reliable bioavailability and easier titration. It is better to start insulin infusions several hours before surgery, as the patient's insulin sensitivity and dosage requirements can be better evaluated. Patients undergoing cardiac and neurologic surgery require "tight" glycemic control with normoglycemic levels in the 80-110 mg/dL range. The targets for glycemic control are less clear in other clinical settings.

Resumption of the patient's preoperative drug regimen should be reevaluated prior to discharge from hospital.