Insulin and Other Glucose-Lowering Drugs

I. OVERVIEW

The pancreas is both an endocrine gland that produces the peptide hormones insulin, glucagon, and somatostatin and an exocrine gland that produces digestive enzymes. The peptide hormones are secreted from cells located in the islets of Langerhans (β cells produce insulin, α cells produce glucagon, and δ cells produce somatostatin). Hyperinsulinemia cause severe hypoglycemia. Diabetes mellitus can cause serious hyperglycemia. If this condition is left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result. Administration of insulin preparations or other injectable or oral glucoselowering agents can prevent morbidity and reduce mortality associated with diabetes.

II. DIABETES MELLITUS

Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by an elevation of blood glucose caused by a relative or absolute deficiency of insulin. The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: type 1 diabetes (formerly, insulin-dependent diabetes mellitus), type 2 diabetes (formerly, non-insulin-dependent diabetes mellitus), gestational diabetes, and diabetes due to other causes (for example, genetic defects or medications). Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during pregnancy. It is important to maintain adequate glycemic control during pregnancy, because uncontrolled gestational diabetes can lead to fetal macrosomia (abnormally large body) and shoulder dystocia (difficult delivery), as well as neonatal hypoglycemia. Diet, exercise, and/ or insulin administration are effective in this condition.

A. Type 1 diabetes

Type 1 diabetic shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss). Type 1 diabetics require exogenous insulin to avoid the catabolic state that results from and is characterized by hyperglycemia and life-threatening ketoacidosis.
1. **Cause of type 1 diabetes**: The development and progression of neuropathy, nephropathy, and retinopathy are directly related to the extent of glycemic control (measured as blood levels of glucose and/or hemoglobin A1c [HbA1c]).

2. **Treatment**: A person with type 1 diabetes must rely on exogenous (injected) insulin to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA1c). The goal in administering insulin to those with type 1 diabetes is to maintain blood glucose concentrations as close to normal as possible and to avoid long-term complications. Continuous subcutaneous insulin infusion (also called the insulin pump) is another method of insulin delivery. Other methods of insulin delivery, such as transdermal, buccal, and intranasal, are currently under investigation.

**B. Type 2 diabetes**

Most diabetic patients have type 2 disease. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than by autoimmune processes or viruses.

1. **Cause**: In type 2 diabetes, the pancreas retains some β-cell function, but variable insulin secretion is insufficient to maintain glucose homeostasis. Type 2 diabetes is frequently accompanied by the lack of sensitivity of target organs to either endogenous or exogenous insulin. This resistance to insulin is considered to be a major cause of this type of diabetes.

2. **Treatment**: The goal in treating type 2 diabetes is to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease. Weight reduction, exercise, and dietary modification decrease insulin resistance and correct the hyperglycemia of type 2 diabetes in some patients. However, most patients are dependent on pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β-cell function declines and insulin therapy is often required to achieve satisfactory serum glucose levels.

**III. INSULIN AND ITS ANALOGS**

Insulin is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin and C-peptide. Measurement of circulating C-peptide provides a better index of insulin levels.
A. Insulin secretion

Insulin secretion is regulated not only by blood glucose levels but also by certain amino acids, other hormones, and autonomic mediators. Secretion is most commonly triggered by high blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a block of K+ channels, leading to membrane depolarization and an influx of Ca2+. The increase in intracellular Ca2+ causes pulsatile insulin exocytosis. The sulfonylureas and glinides owe their hypoglycemic effect to the inhibition of K+ channels.

B. Sources of insulin

Human insulin is produced by recombinant DNA technology using special strains of Escherichia coli or yeast that have been genetically altered to contain the gene for human insulin. Modifications of the amino acid sequence of human insulin have produced insulins with different pharmacokinetic properties. For example, three such insulins, lispro, aspart, and glulisine, have a faster onset and shorter duration of action than regular insulin, because they do not aggregate or form complexes. On the other hand, glargine and detemir are long-acting insulins and show prolonged, flat levels of the hormone following injection.

C. Insulin administration

Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by subcutaneous injection. [Note: In a hyperglycemic emergency, regular insulin is injected intravenously (IV).] Insulin preparations vary primarily in their onset of activity and in duration of activity. This is due to differences in the amino acid sequences of the polypeptides. Dose, site of injection, blood supply, temperature, and physical activity can affect the duration of action of the various preparations. Insulin is inactivated by insulin-degrading enzyme (also called insulin protease), which is found mainly in the liver and kidney.

D. Adverse reactions to insulin

The symptoms of hypoglycemia are the most serious and common adverse reactions to an excessive dose of insulin. Longterm diabetic patients commonly do not produce adequate
amounts of the counter-regulatory hormones (glucagon, epinephrine, cortisol, and growth hormone), which normally provide an effective defense against hypoglycemia. Other adverse reactions include weight gain, lipodystrophy (less common with human insulin), allergic reactions, and local injection site reactions.

IV. INSULIN PREPARATIONS AND TREATMENT

A. Rapid-acting and short-acting insulin preparations

Four preparations fall into this category: regular insulin, insulin lispro, insulin aspart, and insulin glulisine. Regular insulin is a short-acting, soluble, crystalline zinc insulin. Regular insulin is usually given subcutaneously (or IV in emergencies), and it rapidly lowers blood glucose. Regular insulin, insulin lispro, and insulin aspart are pregnancy category B, and insulin glulisine is pregnancy category C. Because of their rapid onset and short duration of action, the lispro, aspart, and glulisine forms are classified as rapid-acting insulins. These agents offer more flexible treatment regimens and may lower the risk of hypoglycemia. Insulin lispro differs from regular insulin in that lysine and proline at positions 28 and 29 in the B chain are reversed. This results in more rapid absorption after subcutaneous injection than is seen with regular insulin. Consequently, insulin lispro acts more rapidly. Peak levels of insulin lispro are seen at 30 to 90 minutes after injection, as compared with 50 to 120 minutes for regular insulin. Insulin lispro also has a shorter duration of activity. Insulin aspart and insulin glulisine have pharmacokinetic and pharmacodynamic properties similar to those of insulin lispro. They are administered to mimic the prandial (mealtime) release of insulin, and they are usually not used alone but with a longer-acting insulin to ensure proper glucose control. Like regular insulin, they are administered subcutaneously.

B. Intermediate-acting insulin

Neutral protamine Hagedorn (NPH) insulin is a suspension of crystalline zinc insulin combined at neutral pH with the positively charged polypeptide protamine. [Note: Another name for this preparation is insulin isophane.] Its duration of action is intermediate because of the delayed absorption from its conjugation with protamine, forming a less-soluble complex. NPH insulin should only be given subcutaneously (never IV) and is useful in treating all forms of diabetes except diabetic ketoacidosis and emergency hyperglycemia. It is used for basal control and is usually given along with rapid- or short-acting insulin for mealtime control. [Note: A similar compound called
neutral protamine lispro (NPL) insulin has been prepared that is used only in combination with insulin lispro.]

C. Long-acting insulin preparations

1. Insulin glargine: It is slower in onset than NPH insulin and has a flat, prolonged hypoglycemic effect with no peak. Like the other insulins, it must be given subcutaneously.

2. Insulin detemir: Insulin detemir has a fatty-acid side chain. This addition enhances association to albumin. Slow dissociation from albumin results in long-acting properties similar to those of insulin glargine. Neither insulin detemir nor insulin glargine should be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamic and pharmacokinetic properties.

D. Insulin combinations

Various premixed combinations of human insulins, such as 70-percent NPH insulin plus 30-percent regular insulin, 50 percent of each of these, and 75-percent NPL insulin plus 25-percent insulin lispro, are also available.

E. Standard treatment versus intensive treatment

For patients with diabetes mellitus who require insulin therapy, standard treatment involves injection of insulin twice daily. In contrast, intensive treatment seeks to normalize blood glucose through more frequent injections of insulin (three or more times daily in response to monitoring blood glucose levels). The ADA recommends a target mean blood glucose level of 154 mg/dL or less for patients with diabetes, and this is more likely to be achieved with intensive treatment. The frequency of hypoglycemic episodes, coma, and seizures due to excessive insulin is higher with intensive treatment regimens. Nonetheless, patients on intensive therapy show a significant reduction in such long-term complications of diabetes as retinopathy, nephropathy, and neuropathy compared to patients receiving standard care. Intensive therapy has not been shown to significantly reduce the macrovascular complications of diabetes.

V. SYNTHETIC AMYLIN ANALOG

Pramlintide is a synthetic amylin analog that is indicated as an adjunct to mealtime insulin therapy in patients with type 1 and type 2 diabetes. By acting as an
amylinomimetic, pramlintide delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety. Pramlintide is administered by subcutaneous injection and should be injected immediately prior to meals. When pramlintide is initiated, the dose of rapid- or short-acting insulin should be decreased by 50 percent prior to meals to avoid a risk of severe hypoglycemia. Pramlintide may not be mixed in the same syringe with any insulin preparation. Adverse effects are mainly gastrointestinal and consist of nausea, anorexia, and vomiting.

VI. ORAL AGENTS: INSULIN SECRETAGOGUES

These agents are useful in the treatment of patients who have type 2 diabetes but who cannot be managed by diet alone. Patients who have developed diabetes after age 40 and have had diabetes less than 5 years are those most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of glucose-lowering drugs with or without insulin to control their hyperglycemia.

A. Sulfonylureas

These agents are classified as insulin secretagogues, because they promote insulin release from the β cells of the pancreas. The primary drugs used today are the second-generation drugs glyburide, glipizide, and glimepiride.

1. Mechanism of action: The mechanism of action includes 1) stimulation of insulin release from the β cells of the pancreas by blocking the ATP-sensitive K+ channels, resulting in depolarization and Ca2+ influx; 2) reduction in hepatic glucose production; and 3) increase in peripheral insulin sensitivity.

2. Pharmacokinetics and fate: Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted by the liver or kidney. The duration of action ranges from 12 to 24 hours.

3. Adverse effects: Weight gain, hyperinsulinemia, and hypoglycemia. These drugs should be used with caution in patients with hepatic or renal insufficiency, because delayed excretion of the drug and resulting accumulation may cause hypoglycemia. Renal impairment is a particular problem in the case of those agents that are metabolized to active compounds such as glyburide. Glyburide has minimal transfer across the placenta and may be a reasonably safe alternative to insulin therapy for diabetes in pregnancy.
B. Glinides

This class of agents includes repaglinide and nateglinide. Although they are not sulfonylureas, they have common actions.

1. Mechanism of action: Like the sulfonylureas, their action is dependent on functioning pancreatic β cells. They bind to a distinct site on the sulfonylurea receptor of ATP-sensitive potassium channels, thereby initiating a series of reactions culminating in the release of insulin. However, in contrast to the sulfonylureas, the glinides have a rapid onset and a short duration of action. They are particularly effective in the early release of insulin that occurs after a meal and are categorized as postprandial glucose regulators.

2. Pharmacokinetics and fate: These drugs are well absorbed orally. Both glinides are metabolized to inactive products by cytochrome P450 3A4 in the liver and are excreted through the bile.

3. Adverse effects: Although these drugs can cause hypoglycemia, the incidence of this adverse effect appears to be lower than that with the sulfonylureas. Repaglinide has been reported to cause severe hypoglycemia in patients who are also taking the lipid-lowering drug gemfibrozil, and concurrent use is contraindicated. Weight gain is less of a problem with the glinides than with the sulfonylureas. These agents must be used with caution in patients with hepatic impairment.

VII. ORAL AGENTS: INSULIN SENSITIZERS

Two classes of oral agents, the biguanides and thiazolidinediones, improve insulin action. These agents lower blood sugar by improving target-cell response to insulin without increasing pancreatic insulin secretion.

A. Biguanides

Metformin, is classed as an insulin sensitizer. It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance. Metformin differs from the sulfonylureas in that it does not promote insulin secretion. Therefore, the risk of hypoglycemia is far less than that with sulfonylurea agents.

1. Mechanism of action: The main mechanism of action of metformin is reduction of hepatic glucose output, largely by inhibiting hepatic gluconeogenesis. Metformin also slows intestinal absorption of sugars and improves peripheral glucose uptake and
utilization. An important property of this drug is its ability to modestly reduce hyperlipidemia. Metformin as the drug of choice for newly diagnosed type 2 diabetics. Metformin may be used alone or in combination with one of the other agents as well as with insulin.

2. Pharmacokinetics and fate: Metformin is well absorbed orally, is not bound to serum proteins, and is not metabolized. Excretion is via the urine.

3. Adverse effects: These are largely gastrointestinal. Metformin is contraindicated in diabetic patients with renal and/or hepatic disease and in those with diabetic ketoacidosis. It should be discontinued in cases of acute myocardial infarction, exacerbation of congestive heart failure, and severe infection. Metformin should be used with caution in patients older than age 80 years and in those with a history of congestive heart failure or alcohol abuse. Metformin should be temporarily discontinued in patients undergoing -diagnosis d requiring IV radiographic contrast agents. Rarely, potentially fatal lactic acidosis has occurred. Long-term use may interfere with vitamin B12 absorption.

4. Other uses: In addition to the treatment of type 2 diabetes, metformin is effective in the treatment of polycystic ovary disease. Its ability to lower insulin resistance in these women can result in ovulation and, therefore, possibly pregnancy.

B. Thiazolidinediones (glitazones)

Another group of agents that are insulin sensitizers are the thiazolidinediones (TZDs), also called the glitazones. Although insulin is required for their action, these drugs do not promote its release from the pancreatic β cells, so hyperinsulinemia is not a risk. Troglitazone was the first of these to be approved for the treatment of type 2 diabetes but was withdrawn after a number of deaths from hepatotoxicity were reported. The two members of this class currently available are pioglitazone and rosiglitazone.

VIII. ORAL AGENTS: α-GLUCOSIDASE INHIBITORS

Acarbose and miglitol are orally active drugs used for the treatment of patients with type 2 diabetes.

A. Mechanism of action

These drugs are taken at the beginning of meals. They act by delaying the digestion of carbohydrates, thereby resulting in lower post- randial p glucose levels. Both drugs exert
their effects by reversibly inhibiting membrane-bound α-glucosidase in the intestinal brush border. This enzyme is responsible for the hydrolysis of oligosaccharides to glucose and other sugars. [Note: Acarbose also inhibits pancreatic α-amylase, thereby interfering with the breakdown of starch to oligosaccharides.] Consequently, the postprandial rise of blood glucose is blunted. Unlike other oral glucose-lowering agents, these drugs neither stimulate insulin release nor increase insulin action in target tissues.

B. Pharmacokinetics and fate

Acarbose is poorly absorbed. It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine. On the other hand, miglitol is very well absorbed but has no systemic effects. It is excreted unchanged by the kidney.

C. Adverse effects

The major side effects are flatulence, diarrhea, and abdominal cramping. Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

IX. ORAL AGENTS: DIPEPTIDYL PEPTIDASE-IV INHIBITORS

Sitagliptin and saxagliptin are orally active dipeptidyl peptidase-IV (DPP-IV) inhibitors used for the treatment of patients with type 2 diabetes. Other agents in this category are currently in development.

A. Mechanism of action

These drugs inhibit the enzyme DPP-IV, which is responsible for the inactivation of incretin hormones. Prolonging the activity of incretin hormones results in increased insulin release in response to meals and a reduction in inappropriate secretion of glucagon. DPP-IV inhibitors may be used as monotherapy or in combination with a sulfonylurea, metformin, glitazones, or insulin.

B. Pharmacokinetics and fate

The DPP-IV inhibitors are well absorbed after oral administration. Food does not affect the extent of absorption. The majority of sitagliptin is excreted unchanged in the urine. Saxagliptin is metabolized via CYP450 3A4/5 to an active metabolite. The primary route
of elimination for saxagliptin and the metabolite is renal. Dosage adjustments for both DPPIV inhibitors are recommended for patients with renal dysfunction.

C. Adverse effects

In general, DPP-IV inhibitors are well tolerated, with the most common adverse effects being nasopharyngitis and headache. Rates of hypoglycemia are comparable to those with placebo when these agents are used as monotherapy or in combination with metformin or pioglitazone. Pancreatitis has occurred with use of sitagliptin. Strong inhibitors of CYP450 3A4/5, such as nelfinavir, atazanavir, ketoconazole, and clarithromycin, may increase levels of saxagliptin. Therefore, reduced doses of saxagliptin should be used.

X. INCRETIN MIMETICS

Oral glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV. This effect is referred to as the “incretin effect” and is markedly reduced in type 2 diabetes. The incretin effect occurs because the gut releases incretin hormones, notably GLP-1 and glucosedependent insulinotropic polypeptide, in response to a meal. Incretin hormones are responsible for 60 to 70 percent of postprandial insulin secretion. Exenatide [EX-e-nah-tide] and liraglutide [LIR-a-GLOO-tide] are injectable incretin mimetics used for the treatment of patients with type 2 diabetes. These agents may be used as adjunct therapy in patients who have failed to achieve adequate glycemic control on a sulfonylurea, metformin, a glitazone, or a combination thereof.

A. Mechanism of action

The incretin mimetics are analogs of GLP-1 that exert their activity by acting as GLP-1 receptor agonists. These agents not only improve glucose-dependent insulin secretion but also slow gastric emptying time, decrease food intake, decrease postprandial glucagon secretion, and promote β-cell proliferation. Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA1c levels decline.

B. Pharmacokinetics and fate

Being polypeptides, exenatide and liraglutide must be administered subcutaneously. Liraglutide is highly protein bound and has a long halflife, allowing for once-daily dosing without regard to meals. Exenatide is eliminated mainly via glomerular filtration and has a much shorter halflife. Because of its short duration of action, exenatide should be
injected twice daily within 60 minutes prior to morning and evening meals. A once-weekly preparation is under investigation. Exenatide should be avoided in patients with severe renal impairment.

C. Adverse effects

Similar to pramlintide, the main adverse effects of the incretin mimetics consist of nausea, vomiting, diarrhea, and constipation. Because of the peptide nature of incretin mimetics, patients may form antibodies to these agents. In most cases the antibodies do not result in reduced efficacy of the drug or increased adverse effects. Exenatide and liraglutide have been associated with pancreatitis. Patients should be advised to discontinue these agents and contact their healthcare provider immediately if they experience severe abdominal pain. Liraglutide causes thyroid C-cell tumors in rodents. However, it is unknown if it causes these tumors or thyroid carcinoma in humans.