67 Insulin and Oral Drugs for Diabetes Mellitus

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DRUG LIST

GENERIC NAME	PAGE	GENERIC NAME	PAGE
Acarbose	775	Metformin	773
Acetohexamide	772	Miglitol	775
Chlorpropamide	772	Nateglinide	773
Glargine	769	Pioglitazone	774
Glimeperide	773	Repaglinide	773
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GLUCOSE HOMEOSTASIS

Carbohydrates, particularly glucose, are an important source of fuel for living organisms. Glucose is a major energy source for all cells, and some tissues (e.g., brain) need a continuous delivery of glucose. Maintenance of serum glucose concentrations within a normal physiological range, critical to the maintenance of normal fuel use, is primarily accomplished by two pancreatic hormones, insulin and glucagon. Derangements of glucagon or insulin regulation can result in hyperglycemia or hypoglycemia, respectively.

Glucose penetrates most tissues slowly unless insulin is present to facilitate its uptake; however, central nervous system (CNS) cells, capillary endothelial cells, gastrointestinal epithelial cells, pancreatic cells, and renal medullary cells are freely permeable to glucose.

The endocrine portion of the pancreas, called the *islets of Langerhans,* consists of cordlike groups of cells arranged along pancreatic capillary channels. Two major types of secretory cells exist within the islets: α-cells, which produce glucagon; and β-cells, which produce insulin. Other cell types are also present in the islets, including the δ-cells, which secrete somatostatin, and PP cells, which produce pancreatic polypeptide. These pancreatic cells monitor changes in the availability of small calorigenic molecules, namely glucose, and to a lesser extent amino acids, ketone bodies, and fatty acids. Pancreatic β-cells appropriately alter their rates of insulin secretion in response to fluctuations in the levels of these calorigenic molecules, with *glucose playing the dominant role in regulation of insulin secretion.* Pancreatic α-cells secrete glucagon in response to increases in amino acid and fatty acid levels; however, glucose inhibits glucagon secretion. If blood glucose levels fall (e.g., during hypoglycemia or fasting), glucagon secretion is augmented, providing a counterregulatory hormonal response that stimulates

gluconeogenesis in the liver and other tissues to avoid hypoglycemia.

Blood glucose concentrations are strictly maintained within homeostatic limits by a variety of biochemical and physiological control mechanisms. Circulating glucose levels are determined by the balance among absorption, storage, production, and use (metabolic rate). *Glucagon* and *insulin* are the two most important hormones that maintain glucose homeostasis when blood concentrations are perturbed.

INSULIN

More than a century has passed since von Mering and Minkowski first demonstrated that pancreatectomized dogs exhibited signs and symptoms characteristic of diabetes mellitus. Shortly thereafter, Banting and Best used pancreatic extracts to reverse these symptoms in diabetic patients, thus providing a basis for establishing a cause-and-effect relationship between insulin deficiency and diabetes. Insulin was subsequently isolated, crystallized, and eventually synthesized in the laboratory. Insulin replacement therapy has been widely used in the clinical management of diabetes mellitus for more than 70 years. In 1982, recombinant DNA (rDNA) derived *human insulin* was first produced and is now widely used instead of insulin derived from beef or pork. More recently, insulin analogues have been produced that modulate the activity and rate of insulin action.

Chemistry

Insulin is a relatively simple protein consisting of 51 amino acids arranged as two polypeptide chains, an α-chain and β-chain, connected by disulfide bonds; the latter are necessary to maintain tertiary structure and biological activity (Fig 67.1). Although the amino acid

sequence and composition of animal insulins may differ slightly from those of human insulin, their biological actions are similar. Alteration of specific amino acid residues within the insulin molecule yields novel derivatives that vary in their pharmacokinetics and binding affinity for the insulin receptor. Some insulin analogues display mitogenic properties in addition to their metabolic effects.

Biosynthesis and Secretion

The insulin molecule is initially translated in pancreatic β-cells as a large single-chain polypeptide called *preproinsulin,* then further processed to *proinsulin* by specific endopeptidases and packaged into storage granules prior to release. Proinsulin has little inherent biological activity and must be converted to insulin by the action of specific proteases in the Golgi apparatus; this enzyme action results in the formation of insulin and *C* (*connecting*) *peptide.* C-peptide facilitates the correct folding of the α- and β-chains of insulin and maintains the alignment of the disulfide bridges in insulin before cleavage of the C-peptide from insulin. Both insulin and C-peptide are stored in the pancreatic β-cell granules, and both are liberated during insulin secretion. Though it is unclear whether C-peptide has any function after it enters the circulation, it is sometimes measured as an indicator of endogenous insulin production.

The specific stimulus for insulin release involves fluctuations in the serum glucose levels and to a much lesser extent levels of other substrates. Glucose enters the pancreatic β-cell via glucose transporter isoform (GLUT) 4 glucose transporters, is quickly phosphorylated to glucose-6-phosphate, and triggers an intracellular influx of calcium ions that promotes fusion of the insulin-containing secretory granules with the cell membrane (*exocytosis*).

Insulin is continuously secreted at a low basal level during fasting, but a postprandial rise in serum glucose or amino acid levels can augment blood levels of insulin severalfold. Other nutrients (e.g., arginine, leucine) and several hormones (e.g., glucagon, growth hormone, secretin, gastrin cholecystokinin, pancreozymin, adrenocorticotropin) modulate insulin release. The autonomic nervous system also participates in the regulation of the rate of insulin secretion, with the islets of Langerhans receiving both cholinergic and adrenergic innervation. Insulin secretion is enhanced by vagal (cholinergic) and diminished by sympathetic (adrenergic) stimulation.

Glucose-induced stimulation of insulin release from cells is biphasic. The initial rapid rise in insulin that follows a rise in glucose is termed the first phase of insulin release and is thought to reflect the release of the presynthesized insulin in the storage granules; a more delayed and prolonged rise in insulin secretion follows. This second phase of insulin secretion is due to an upregulation of insulin expression and production. The first phase of insulin secretion is often blunted in diabetes.

Biochemical and Pharmacological Actions of Insulin

The biochemical actions of insulin are complex and involve many steps to integrate carbohydrate, protein, and lipid metabolism for the maintenance of fuel homeostasis. In addition to its effects on stimulating glucose uptake by tissues, insulin has five major physiological effects on fuel homeostasis. It can (1) diminish hepatic glycogenolysis by inhibiting glycogen phosphorylase; (2) promote hepatic glucose storage into glycogen by stimulating glycogen synthetase; (3) inhibit hepatic gluconeogenesis (i.e., convert noncarbohydrate substrates like amino acids into glucose); (4) inhibit lipolysis by inhibiting hormone-sensitive lipase activity, thereby decreasing plasma free fatty acid and glycerol levels; and (5) promote the active transport of amino acids into cells for incorporation into protein, thereby producing a net positive nitrogen balance.

The biological actions of insulin are initiated following a reversible binding of the hormone to a high-affinity specific insulin receptor on the cell membrane surface (Fig. 67.2). The insulin receptor is a heterotetrameric tyrosine kinase receptor composed of two α- and two β-subunits. Insulin binds to the α-subunit on the extracellular surface of the cell and activates tyrosine kinase activity in the intracellular portion of the β-subunit. This results in the autophosphorylation of the adjacent insulin β-receptor subunit and the phosphorylation of tyrosine residues on cytoplasmic proteins, termed the insulin receptor substrate (IRS) 1 and 2. IRS phosphorylation provides a docking site for other intracellular signaling proteins. The regulatory subunit of phosphatidyl inositol 3 (PI-3) kinase (p85) becomes activated and dimerizes with its catalytic subunit (p110), and this complex mobilizes the translocation of glucose transporters to the cell membrane surface, which promotes hexose transport. Other downstream signaling pathways include activation of p70-S6 kinase, protein kinase B (both via PI-3 kinase), and Grb2 activation of the Ras-Raf-MAP kinase pathway, which controls glycogen synthesis and cell growth. The hormone–receptor complex may then be internalized by endocytosis, which results in degradation of insulin and recycling of the receptor to the cell membrane surface.

Absorption, Metabolism, and Excretion

Insulin is usually administered subcutaneously. Depending on the type of insulin being administered, the rate of insulin absorption can be modulated by al-

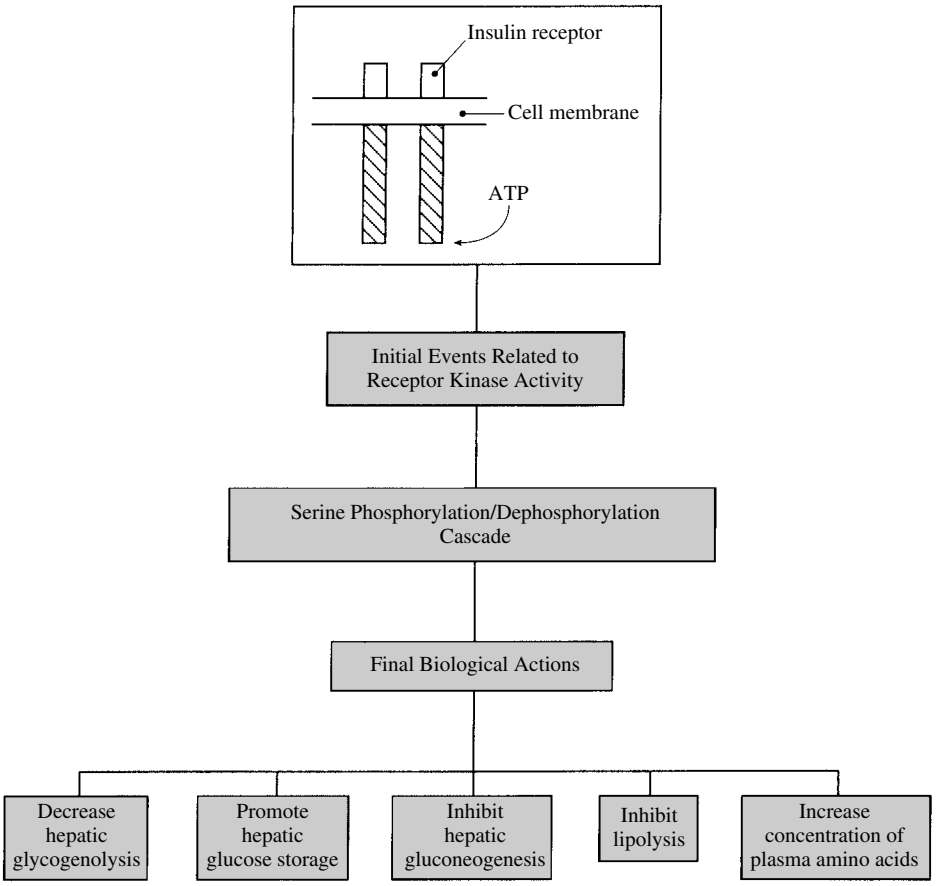

FIGURE 67.2
Levels of insulin action. Insulin acts in stages, with the initial events related to receptor tyrosine kinase activity. The second stage is a cascade of serine phosphorylation and dephosphorylation reactions involving the enzyme MAP (mitogen-activated protein–microtubule-associated protein kinase). The final stage includes the glucose transport molecules themselves, enzymes for glycogen and lipid synthesis, and proteins involved in the hormone's action on gene expression and cell growth.

tering the polymerization of the insulin molecule (e.g., monomers, dimers, or hexamers). Intramuscular injections of insulin are used less often because absorption is more rapid. Being a polypeptide hormone, insulin is readily inactivated if administered orally. In emergencies, such as severe diabetic ketoacidosis, insulin can be given intravenously. Clinical studies are examining the efficacy and safety of inhaled insulin, which may be promising for some patients.

Once insulin enters the circulation, its plasma half-life is less than 10 minutes. Hepatic insulinases destroy approximately 50% of circulating insulin, with the remainder degraded by circulating proteases. Therefore, only a relatively small amount of the total endogenous insulin secreted ever reaches the peripheral tissues. Although a number of tissues accumulate small amounts of insulin, *the liver and kidney are the principal sites of hormone uptake and degradation.* Insulin metabolism is accomplished both through the actions of an insulin-specific protease found in the cytosol of many tissues and by the reductive cleavage of the insulin disulfide bonds by glutathione–insulin transhydrogenase. In the kidney, insulin that undergoes glomerular filtration is almost completely reabsorbed and metabolized within the proximal convoluted tubules of the nephron.

DIABETES MELLITUS

Diabetes mellitus affects approximately 5 to 8% of the population. A large number of individuals are asymptomatic and do not know they have the disease. The recent rise in obesity in the United States accounts for much of the observed and anticipated rise in cases of diabetes mellitus in this country. Although insulin treatment has greatly increased the life expectancy of the diabetic patient, diabetes remains the third leading cause

of death by disease, the second leading cause of blindness, and the second leading cause of renal failure.

Diabetes mellitus is a heterogeneous group of disorders characterized by abnormalities in carbohydrate, protein, and lipid metabolism. The central disturbance in diabetes mellitus is an abnormality in insulin production or action or both, although other factors can be involved. Hyperglycemia is a common end point for all types of diabetes mellitus and is the parameter that is measured to evaluate and manage the efficacy of diabetes therapy.

Diabetes mellitus has been traditionally classified into *insulin-dependent* diabetes mellitus (IDDM), also known as type I (formerly called juvenile-onset diabetes mellitus), and *non–insulin-dependent* diabetes mellitus (NIDDM), also known as type II (formerly referred to as adult-onset diabetes mellitus). There are clearly varying degrees of overlap, and though it is often important to know whether a particular individual possesses relative insulin deficiency or relative insulin resistance or both, some of the more salient differences between IDDM and NIDDM are summarized in Table 67.1.

The pathogenesis of type I diabetes is autoimmune destruction of the cells of the pancreas. The factor or factors that trigger this autoimmune response are unknown. Predisposing factors appear to include certain major histocompatibility complex haplotypes and autoantibodies to various islet cell antigens. The progression of the autoimmune response is characterized by lymphocytic infiltration and destruction of the pancreatic cells resulting in insulin deficiency. Type I diabetes mellitus constitutes about 10% of cases of diabetes mellitus.

The other type of diabetes mellitus, type II, is far more common. In contrast, type II is not an autoimmune process and may or may not be insulin dependent; that is, a diabetic state that is most effectively managed by insulin therapy. Frequently, NIDDM is used interchangeably with type II diabetes mellitus, and efforts are being made to avoid the term adult onset, since many adolescents (and occasionally children) are developing NIDDM. Because the incidence of diabetes is high in families of persons with NIDDM, a strong genetic predisposition is suspected. However, NIDDM is most likely a polygenic disease, involving multiple genetic predispositions to the development of the diabetic state.

The three major metabolic abnormalities that contribute to hyperglycemia in NIDDM are defective glucose-induced insulin secretion, increased hepatic glucose output, and inability of insulin to stimulate glucose uptake in peripheral target tissues. These abnormalities also involve the cellular glucose transport in cells, liver, adipose tissue, and skeletal muscle, and they may be the result of alterations in GLUTs. Another essential problem in NIDDM may be reduced sensitivity of fat and muscle cells to the effects of insulin (i.e., *insulin resistance*). Consequently, in early stages of NIDDM, the pancreas may produce normal or even excessive amounts of insulin and only become impaired at insulin production at a later stage of the disease. Recently, a hormone produced in adipose tissue, *resistin,* has been identified and is postulated to cause many of the derangements that ultimately result in insulin resistance.

Several putative sites of insulin resistance have been identified in humans, including a defective binding of insulin to a receptor and a blunting of insulin signal transduction. Conditions associated with elevated insulin levels (*hyperinsulinism*), such as obesity, may be the result of *down-regulation* in the number of insulin receptors, effectively resulting in a state of insulin resistance. Conversely, decreases in insulin levels (e.g., diabetes) may lead to an *up-regulation* of the receptors, which may shift the insulin dose–response curve to the left; that is, less insulin would be required to produce a given biological effect. The extent to which receptor regulation actually participates in adjustments to changing physiological conditions has not been definitively established.

TABLE 67.1 Features of Type I and Type II Diabetes Mellitus

Characteristic	Type I	Type II
Onset (age)	Usually <30	Usually >40
Type of onset	Abrupt	Gradual
Nutritional status	Often thin	Often obese
Clinical symptoms	Polydipsia, polyuria, polyphagia	Often asymptomatic
Ketosis	Present	Usually absent
Endogenous insulin	Absent	Variable
Insulin therapy	Required	Sometimes
Oral hypoglycemics	Usually not effective	Often effective
Diet	Mandatory with insulin	Mandatory with or without drugs

Insulin resistance also has been associated with a number of hormonal and metabolic states, including Cushing's syndrome (excessive corticosteroids), acromegaly (excessive growth hormone), and gestational diabetes. Physiological or psychological stress also can contribute to insulin resistance. *Gestational diabetes mellitus* is a condition that develops during the second trimester of pregnancy; the cause may be rises in human placental lactogen and other hormones that contribute to insulin resistance. This condition usually resolves during the postpartum period. Another relatively common form of insulin resistance is often seen in women with *polycystic ovarian syndrome,* a disorder that is associated with hyperandrogenism, hirsutism, menstrual irregularities, obesity, and infertility.

METABOLIC DISTURBANCES AND COMPLICATIONS OF THE DIABETIC STATE

There are only two major sources of blood glucose: *exogenous,* or the ingestion of dietary carbohydrate, and *endogenous,* which is contributed by hepatic and renal gluconeogenesis and hepatic glycogenolysis. *Diabetes mellitus is a metabolic disorder in which carbohydrate metabolism is reduced while that of proteins and lipids is increased.* In diabetics, exogenous and endogenous glucose is not used effectively, and it accumulates in the blood (*hyperglycemia*). As blood glucose levels increase, the amount of glucose filtered by the glomeruli eventually exceeds the reabsorption capacity (T_m, transport maximum) of the proximal tubule cells, and glucose appears in the urine (*glucosuria*). Protein catabolism and the rate of nitrogen excretion are increased when blood insulin falls to low levels; stimulation of hepatic gluconeogenesis converts amino acids to glucose. The catabolism of lipids and fatty acids is also accelerated in the absence of insulin, leading to the formation of *ketone bodies,* such as acetoacetic acid, β-hydroxybutyric acid, and acetone. Renal losses of glucose, nitrogenous substances, and ketone bodies promote osmotic diuresis that can result in dehydration, electrolyte abnormalities, and acid–base disturbances. *Diabetic ketoacidosis* is the end result of insulin deficiency in uncontrolled type I diabetes.

Type II diabetics are less prone to develop ketone bodies or diabetic ketoacidosis but may develop *hyperosmolar coma,* a condition characterized by severe hyperglycemia and dehydration. Both diabetic ketoacidosis and hyperosmolar coma are medical emergencies that require prompt insulin administration and intravenous fluids.

Diabetes mellitus is associated with many complications that are increased in the setting of poor glycemic control. Diabetes mellitus can cause microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) and macrovascular complications (e.g., atherosclerotic cardiovascular disease), associated with diabetic dyslipidemia (usually elevated triglycerides and low-density lipoprotein cholesterol). Recent clinical trials have demonstrated that the risk of developing chronic complications of diabetes is reduced by achieving good glycemic control. This can be accomplished by a combination of diet, exercise, and rational pharmacological therapy directly targeted to optimize diabetes management.

CLINICAL MANAGEMENT OF DIABETES

Diet is the cornerstone of the management of diabetes, regardless of the severity of the symptoms or the type of diabetes. Exercise is also an important component in managing diabetes, particularly in obese individuals with NIDDM who may have a component of insulin resistance as a consequence of obesity. Treatment regimens that have proved effective include a calorie-restricted diet in combination with exogenous insulin or oral hypoglycemic drugs. However, since diet, exercise, and oral hypoglycemic drugs (Table 67.2), often because of noncompliance by the patient, will not always achieve the clinical objectives of controlling the symptoms of diabetes, insulin remains universally important in therapeutic management. The administration of insulin is required for the treatment of type I (IDDM) and in cases of type II (NIDDM) that are refractory to management with oral hypoglycemic drugs.

Because the spectrum of patients with diabetes extends from the totally asymptomatic individual to one with life-threatening ketoacidosis, *therapeutic management must be highly individualized.* An important objective is to maintain a glucose level as close to normal as possible without producing frequent hypoglycemia or overly restricting the patient's lifestyle. Many diabetics aim to achieve an average blood glucose below 150 (hemoglobin A1c $< 7\%$). Unstable or ketoacidosis-prone diabetics are difficult to maintain with a single dose of either intermediate- or long-acting insulin; they usually require multiple injections of combinations of short-, intermediate-, and/or long-acting insulin preparations.

Insulin Preparations

Commercially available insulins differ in their onset of action, maximal activity, and duration of action (Table 67.3). They can be classified as *rapid acting* (0–5 hours), *short acting* (0–8 hours), *intermediate acting* (2 to 16 hours), and *long acting* (4 to 36 hours). Human insulin (e.g. *Humulin, Novolin*) produced by rDNA technology is now widely available and has largely supplanted in-

TABLE 67.2 Antidiabetic Drugs

Augment Insulin Supply	Enhance Insulin Action	Delay Carbohydrate Absorption
Sulfonylureas	Biguanides	α-Glucosidase inhibitors
Meglitinides	Thiazolidine-diones	
Insulins		

sulins derived from beef and pork. Some insulins have been modified through genetic engineering to produce insulin analogues, derivatives that possess novel pharmacokinetic properties (lispro, insulin aspart, and insulin glargine). The duration of action can vary with factors such as injection volume, injection site, and blood flow at the site of administration.

Rapid-acting insulin analogues (lispro, insulin aspart [*Humalog, Novolog*]) have been engineered to contain amino acid modifications that promote rapid entry into the circulation from subcutaneous tissue. They begin to exert their effects as early as 5 to 10 minutes after administration. Lispro insulin, the first insulin analogue to be approved in Europe and the United States, is produced by switching the positions of lysine-proline amino acid residues 28 and 29 of the carboxy terminus of the β-chain. Lispro insulin displays very similar actions to insulin and has a similar affinity for the insulin receptor, but it cannot form stable hexamers or dimers in subcutaneous tissue, which promotes its rapid uptake and absorption.

Insulin aspart is absorbed nearly twice as fast as regular insulin. In addition to binding to the insulin receptor, insulin aspart also binds to the insulinlike growth factor (IGF-1) receptor, which shares structural homology with the insulin receptor. However, at physiological and pharmacological levels, the metabolic effects of insulin aspart predominate. Both lispro insulin and insulin aspart have relatively fast onsets and short half-lives, making them ideal for controlling the upward glycemic excursions that occur immediately after meals in diabetics.

Short-acting or *regular* insulins (*Humulin R, Novolin R*) take 30 minutes to begin to exert their effect but have a longer duration of action than does either lispro insulin or insulin aspart. Typically, regular insulin is administered several minutes before a meal; it has a more gradual onset of action and is designed to control postprandial hyperglycemia. Regular insulin is primarily used to supplement intermediate- and long-acting insulin preparations; however, it is also the preparation of choice for glucose management during surgery, trauma, shock, or diabetic ketoacidosis. Regular insulin can be given intravenously when emergency diabetes management is required (e.g., diabetes ketoacidosis). Prompt insulin zinc suspension (*Semilente*) is also a fast-acting form of insulin, but unlike regular insulin, it should be mixed only with *Lente* or *Ultralente* insulin preparations. Rapid-acting and short-acting insulins are often administered two to three times a day or more. These insulins are also employed in sliding scale insulin regimens, which supplement a person's glucose control based on blood glucose monitoring equipment.

Intermediate-acting preparations (e.g., isophane insulin suspension [*NPH* insulin] or insulin zinc suspension [*Lente* insulin]) have a more delayed onset of action, but they act longer. Conjugation of the insulin molecule with either *zinc* or *protamine* or both will convert the normally rapidly absorbed parenterally administered insulin to a preparation with a longer duration of action. Isophane insulin suspension (*Neutral protamine Hagedorn, NPH*) has a rate of absorption that has been slowed by complexing insulin with protamine, a polyvalent cation. Both NPH and *Lente* insulin are used to control diabetes in a variety of situations except during emergencies (e.g., diabetic ketoacidosis). Intermediate-acting insulin preparations are usually given once or twice a day.

TABLE 67.3 Pharmacokinetic Properties of Insulin Formulations and Analogues

Drug	Onset	Peak	Duration
Short Acting			
Lispro (Humalog)	10–20 min	1–2 hr	2–4 hr
Insulin Aspart (Novolog)	10–20 min	1 hr	3–5 hr
Regular	30–60 min	2–3 hr	5–7 hr
Prompt Insulin Zn Suspension (Semi-Lente)	30–60 min	2–3 hr	5–7 hr
Intermediate Acting			
Isophane Insulin Suspension (NPH)	1–2 hr	5–7 hr	13–18 hr
Insulin Zn Suspension (Lente)	1–3 hr	4–8 hr	13–20 hr
Long Acting			
Extended Zn Suspension (Ultralente)	2–4 hr	8–14 hr	18–36 hr
Insulin Glargine (Lantus)	2–hr	None	up to 24 hr

Protamine zinc and extended insulin zinc suspension (*Ultralente*) are often referred to as *long-acting* insulin preparations. These insulins have more protamine and zinc in the mixture than is found in isophane insulin suspension. Insulin zinc suspension, extended (*Ultralente Insulin*), is quite similar to the protamine zinc insulin suspension except that it does not contain protamine. Both of these long-acting insulins have an approximate duration of action of 36 hours.

Insulin glargine (*Lantus*) is a long-acting insulin analogue that does not use zinc or protamine to modulate insulin solubility. The introduction of two positive arginine residues at the carboxy terminus of the β-chain shifts the isoelectric point of the peptide from 5.4 to 6.7, thus creating a molecule that is soluble at pH 4 but less soluble at neutral (physiological) pH (in subcutaneous tissue). A second modification of insulin, glargine, involves the substitution of a charge-neutral glycine for a negatively charged asparagine at the amino terminal end of the α-chain; this prevents deamidation and dimerization and enhances stability at physiological pH. Injection of insulin glargine forms microprecipitates in subcutaneous tissue as the pH is raised from 4 to physiological. A steady, sustained release of insulin from the site of injection mimics the basal secretion of insulin from the pancreas. Absorption of insulin glargine commences within a few hours of injection, and there is usually little or no peak or trough in the levels of insulin glargine as it dissolves from its site of injection. Because it is necessary to maintain its acidic pH prior to injection, insulin glargine must not be mixed with any other form of insulin during injection.

Adverse Reactions to Insulin Therapy

The most common side effect associated with insulin therapy is *hypoglycemia,* which may result in such CNS symptoms as tremors, lethargy, hunger, confusion, motor and sensory deficits, seizures, and unconsciousness. Adrenergic manifestations include anxiety, palpitations, tachycardia, and diaphoresis. In many cases, diabetics are aware that hypoglycemia is developing, and prompt administration of oral carbohydrates (e.g., fruit juice or glucose tablets) can restore normoglycemia. In more severe cases (e.g., unconsciousness, seizures), intravenous glucose or intramuscular glucagon is required to reverse the hypoglycemia.

Another frequent side effect of insulin therapy is weight gain. Some is due to increased caloric storage of glucose by insulin, and some is due to renal sodium retention resulting in fluid retention and edema. These effects can synergize with oral agents that are often coadministered with insulin, particularly sulfonylureas and thiazolidinediones.

Other complications arising from insulin therapy are uncommon. Sometimes, diabetics treated with exogenous insulin develop insulin-binding immunoglobulins, although the clinical significance of these antibodies remains unclear. Allergic reactions due to the use of animal-derived insulins has subsided since the use of recombinant DNA-derived human insulin became widespread. Over time, repeated subcutaneous injections of insulin can cause local lipodystrophy (lipohypertrophy or lipoatrophy), which may alter the pharmacokinetics of insulin absorption from this site. Also, hypokalemia can follow acute insulin administration, an effect that is due to the stimulation of Na^+–K^+–ATPase (adenosine triphosphatase) with its resultant redistribution of K^+ to the intracellular compartment. This property of insulin is sometimes used in the emergency treatment of *hyperkalemia.*

Insulin Regimens

The rational design of insulin regimens involves estimates and consideration of the patient's diet, lifestyle, level of physical activity, and type of diabetes. A thin, active type I diabetic will have very different insulin requirements from those of a sedentary, obese type II diabetic. Hence, it is not possible to provide a cookbook approach for designing all diabetes regimens. There is usually less insulin resistance in type I diabetics, and it is possible to estimate metabolic needs of insulin based on the type I diabetic patient's weight (typically 0.5 to 1 units/kg/day). Other considerations, such as work schedule and mealtimes, are important in determining the way the insulin is divided proportionally to cover short-range and long-range glycemic control. Although there is quite a bit of variation, most diabetics have about half to two-thirds of their insulin as a long-acting preparation, and the rest is usually delivered as a rapid- or short-acting insulin.

Some insulin preparations are combinations of NPH and *regular* insulin packaged in premixed ratios of 70:30 or 50:50 of NPH and *regular* insulin (*70/30 Humulin, 70/30 Novolin, 50/50 Humulin*). A similar combination product is 75/25 insulin, which contains 75% protamine lispro and 25% lispro insulin. Insulin zinc suspension (*Lente* insulin) is an intermediate-acting mixture of prompt insulin zinc suspension (30%) and extended insulin zinc suspension (70%). While these combination products may be convenient for some patients and can improve compliance, they are not ideal regimens for most diabetics, who may achieve better control by separately mixing their rapid- or short-acting insulin with an intermediate- or long-acting insulin to arrive at a ratio that is better suited to manage their diabetes.

Insulin pumps are small, portable devices worn externally that deliver a continuous supply of insulin subcutaneously through a hypodermic needle. The pumps provide a basal rate of insulin between meals and can be manually adjusted to facilitate glycemic control at

mealtimes. Rapid and short-acting insulins are typically used in insulin pumps. Pumps are usually worn 2 to 3 days before the tubing and needle are changed.

ORAL AGENTS FOR TREATING DIABETES MELLITUS

Although insulin has the disadvantage of having to be injected, it is without question the most uniformly effective treatment of diabetes mellitus. Some milder forms of diabetes mellitus that do not respond to diet management or weight loss and exercise can be treated with oral hypoglycemic agents. The success of oral hypoglycemic drug therapy is usually based on a restoration of normal blood glucose levels and the absence of glycosuria. Traditionally, the term *oral hypoglycemic* was used interchangeably with sulfonylureas, but more recently the development of several new drugs has broadened this designation to include all oral medications for diabetes. Because these drugs do not have to be injected, oral agents enhance compliance in type II diabetics. These classes of drugs are not generally used in type I diabetes. The pharmacokinetic profile of oral agents for diabetes is depicted in Table 67.4.

Sulfonylureas

Sulfonylureas are the most widely prescribed drugs in the treatment of type II diabetes mellitus. The initial sulfonylureas were introduced nearly 50 years ago and were derivatives of the antibacterial sulfonamides. Although their structural similarities to the sulfonamide antibacterial agents are readily apparent, the sulfonylureas possess no antibacterial activity.

Mechanism of Action

The primary mechanism of action of the sulfonylureas is *direct stimulation of insulin release from the pancreatic β-cells.* In the presence of viable pancreatic β-cells, sulfonylureas enhance the release of endogenous insulin, thereby reducing blood glucose levels. At higher doses, these drugs also decrease hepatic glucose production, and the second-generation sulfonylureas may possess additional extrapancreatic effects that increase insulin sensitivity, though the clinical significance of these pharmacological effects is unclear. These mechanisms are summarized in Table 67.3.

The sulfonylureas are *ineffective* for the management of type I and severe type II diabetes mellitus, since the number of viable β-cells in these forms of diabetes is small. Severely obese diabetics often respond poorly to the sulfonylureas, possibly because of the insulin resistance that often accompanies obesity.

The Sulfonylurea Receptor

The sulfonylurea receptor was identified as an adenosine triphosphate (ATP) sensitive potassium (K_{ATP}) channel that is present on the β-cell membrane surface. Closure of these K_{ATP} channels causes β-cell membrane

TABLE 67.4 Pharmacokinetic Properties of Oral Hypoglycemic Drugs

Drug	Half-Life (hr)	Duration of Action (hr)	Activity of Metabolites
Sulfonylureas			
First generation			
Acetohexamide	0.8–2.4	12–18	+
Chlorpropamide	24–48	60	+
Tolazamide	4–7	12–24	+
Tolbutamide	3–28	6–12	−
Second generation			
Glyburide	2–4	16–24	±
Glipizide	1–5	12–24 (XL > 24)	−
Glimeperide	5–9	>24	+
Meglitinides			
Repaglinide	1	4–6	−
Nateglinide	1–2	4	−
Biguanides			
Metformin	4–8	18–24	−
α-Glucosidase inhibitors			
Acarbose	2	4–6	±
Miglitol	2	4–6	−
Thiazolidinediones			
Pioglitazone	26–30	days	−
Rosiglitazone	4	days	−

depolarization and triggers the opening of voltage-dependent calcium channels. The influx of calcium into the β-cell triggers insulin granule fusion to the β-cell membrane and insulin release. The intracellular levels of ATP and adenosine diphosphate (ADP) modulate the activity of the K_{ATP} channel, depending on the availability of glucose.

The activity of the K_{ATP} channels is modulated by the direct binding of sulfonylureas to a specific subunit of the K_{ATP} channel called SUR1. SUR1 is a member of the K^+ inwardly rectifying (Kir) 6.0 subfamily of proteins and can bind nucleotides and sulfonylureas with high affinity. Four SUR1 subunits form a complex with four subunits from the Kir 6.2 subfamily and create the pore for K^+ permeation in the pancreatic β-cell. Sulfonylurea binding to SUR1 directly promotes the closure of these K_{ATP} channels, lowering the threshold for glucose-dependent insulin release. Diazoxide (a direct vasodilator discussed in Chapter 20) also binds to SUR1 but keeps the K_{ATP} channels open, raising the threshold for glucose-stimulated insulin secretion and sometimes causing hyperglycemia in patients.

Absorption, Metabolism, and Excretion

Sulfonylureas are readily absorbed from the gastrointestinal tract following oral administration but undergo varying degrees and rates of metabolism in the liver and/or kidney; some metabolites possess intrinsic hypoglycemic activity. Thus, the biological half-lives of the sulfonylureas vary greatly, and a comparison of the drug half-life with the observed duration of action does not always show a good correlation. Sulfonylureas and their metabolites are excreted either renally or in the feces.

Clinical Uses

Sulfonylureas are generally effective in individuals with mild to moderate type II diabetes. The chance for successful glycemic control with sulfonylureas is poor in diabetic patients requiring more than 40 units of insulin per day. When beginning therapy with one of these drugs, a low to intermediate dose is given initially and then gradually increased until the dosage results in normoglycemia. Once the maximum recommended dosage for a particular sulfonylurea is reached, further increasing the dose will not improve glycemic control.

Adverse Effects and Drug Interactions

The most common adverse effect associated with sulfonylurea administration is hypoglycemia, which may be provoked by inadequate calorie intake (e.g., skipping a meal), or increased caloric needs (e.g., increased physical activity). Collectively, sulfonylureas also tend to cause weight gain, which is undesirable in individuals who already are obese. Some of this weight can be due to fluid retention and edema. Less common adverse reactions include muscular weakness, ataxia, dizziness, mental confusion, skin rash, photosensitivity, blood dyscrasias, and cholestatic jaundice. Occasionally, persons who display drug sensitivities to sulfa-containing antibiotics show a cross-reactivity to the sulfonylureas. In this situation, a nonsulfonylurea insulin secretagogue can be used (if desired), such as repaglinide or nateglinide (discussed later). Sulfonylureas are not used in gestational diabetes, which is generally managed by a combination of intensive diet control and insulin.

Since diabetic patients with renal or hepatic disease are particularly vulnerable to hypoglycemia, the sulfonylurea compounds should be avoided in these individuals. A decrease in alcohol tolerance also has been observed in some patients taking sulfonylurea compounds. Since sulfonylureas are highly bound to plasma proteins and are extensively metabolized by microsomal enzymes, coadministration of drugs capable of displacing them from their protein binding sites or inhibiting their metabolism (e.g., sulfonamide antibacterials, propranolol, salicylates, phenylbutazone, chloramphenicol, probenecid, and alcohol) also may potentiate hypoglycemia.

First-Generation Sulfonylureas

The first-generation sulfonylureas are not frequently used in the modern management of diabetes mellitus because of their relatively low specificity of action, delay in time of onset, occasional long duration of action, and a variety of side effects. They also tend to have more adverse drug interactions than the second-generation sulfonylureas. They are occasionally used in patients who have achieved previous adequate control with these agents.

Acetohexamide (*Dymelor*) is the only sulfonylurea with uricosuric activity, an action that may be of benefit in diabetic patients who also have gout.

Chlorpropamide (*Diabinese*) has a relatively slow onset of action, with its maximal hypoglycemic potential often not reached for 1 or 2 weeks. Similarly, several weeks may be required to eliminate the drug after discontinuation of therapy. This drug can cause flushing, particularly when taken with alcohol, and can also cause hyponatremia. This effect has been employed to treat some patients who have partial central diabetes insipidus, an unrelated condition due to a pituitary ADH deficiency.

Tolazamide (*Tolinase*) is an orally effective hypoglycemic drug that causes less water retention than do the other compounds in this class.

Tolbutamide (*Orinase*) is a relatively short-acting compound that may be useful in patients who are prone to hypoglycemia.

Second-Generation Sulfonylureas

The second-generation sulfonylureas display a higher specificity and affinity for the sulfonylurea receptor and more predictable pharmacokinetics in terms of time of onset and duration of action, and they have fewer side effects. Second-generation sulfonylureas may also exert mild diuretic effects on the kidney and are highly protein bound, primarily through nonionic binding (in contrast to the ionic binding observed with the first-generation compounds).

Glyburide (*DiaBeta, Micronase, Glynase*), also known as glibenclamide, is approximately 150 times as potent as tolbutamide on a molar basis and twice as potent as glipizide (discussed later). Glyburide is completely metabolized in the liver to two weakly active metabolites before excretion in the urine. Its average duration of action is 24 hours.

Glipizide (*Glucotrol*) is similar to glyburide, but it is metabolized by the liver to two inactive metabolites; these metabolites and glipizide are renally excreted.

Glimepiride (*Amaryl*) is metabolized to at least one active metabolite. It is quickly absorbed from the gastrointestinal tract within an hour of oral administration and excreted in the urine and feces. Its half-life varies from 5 to 9 hours depending on the frequency of multiple dosing.

Meglitinides

Though structurally unrelated to sulfonylureas, the meglitinide class of hypoglycemic drugs bind to the same K_{ATP} channel as do the sulfonylureas, but it is unclear whether they bind to the same SUR1 subunit within the K_{ATP} complex. As a class, the meglitinides are incapable of stimulating insulin secretion in nutrient-starved β-cells, but in the presence of glucose, they demonstrate hypoglycemic effects by augmenting the release of insulin. Consequently, meglitinides seem relatively unlikely to cause fasting hypoglycemia.

Repaglinide (*Prandin*), a member of the meglitinide class, is approved for monotherapy or in combination with metformin. Repaglinide is taken before each meal, three times a day, and is rapidly absorbed; it is metabolized by the liver and has a half life of an hour. Insulin levels transiently rise postprandially after repaglinide administration but generally return to baseline by the next meal. Although repaglinide does not appear to offer any advantage over the sulfonylureas, it may be helpful in patients with a known allergy to sulfa drugs. Hypoglycemia is the most common side effect.

Nateglinide (*Starlix*), a newer drug in the meglitinide class, is a phenylalanine derivative that also works by binding to a specific site on the K^+–ATP–sensitive channel on the surface of β-cells. Nateglinide binds with a higher affinity than does repaglinide and has a faster onset of action and a shorter duration of action. Like repaglinide, it is approved for both monotherapy and in combination with metformin. Nateglinide is taken three times a day before meals and achieves peak plasma levels within an hour. Nateglinide administration results in plasma insulin levels that peak within 2 hours; they return to baseline by 4 hours. Nateglinide is metabolized by the liver and excreted by the kidney. The main side effect of nateglinide is hypoglycemia, though its effects on fasting insulin levels is not substantially reduced.

Biguanides

Biguanides are a group of oral hypoglycemic agents that are chemically and pharmacologically distinct from the sulfonylureas. One biguanide, phenformin, was briefly used in the United States more than 30 years ago but was withdrawn from the market because it produced severe lactic acidosis in some patients. Metformin (*Glucophage*) was used in Europe for many years before it was approved for use in the United States in 1995. Metformin is the only approved biguanide for the treatment of patients with NIDDM that are refractory to dietary management alone. Metformin does not affect insulin secretion but requires the presence of insulin to be effective. The exact mechanism of metformin's action is not clear, but it does decrease hepatic glucose production and increase peripheral glucose uptake. When used as monotherapy, metformin rarely causes hypoglycemia.

Metformin works best in patients with significant hyperglycemia and is often considered first-line therapy in the treatment of mild to moderate type II overweight diabetics who demonstrate insulin resistance. The United Kingdom Prospective Diabetes Study demonstrated a marked reduction in cardiovascular comorbidities and diabetic complications in metformin-treated individuals. Metformin has also been used to treat hirsutism in individuals with polycystic ovarian syndrome and may enhance fertility in these women, perhaps by decreasing androgen levels and enhancing insulin sensitivity.

Adverse gastrointestinal symptoms (nausea, vomiting, anorexia, metallic taste, abdominal discomfort, and diarrhea) occur in up to 20% of individuals taking metformin; this can be minimized by starting at a low dose and slowly titrating the dose upward *with food.* Like phenformin, metformin can cause lactic acidosis, but its occurrence is rare except when renal failure, hypoxemia, or severe congestive heart failure is present or when coadministered with alcohol. Metformin is also contraindicated in persons with hepatic dysfunction, but it appears to be safe for use in the hepatic steatosis that often occurs with fatty infiltration of the liver in poorly controlled type II diabetics.

Two relatively new formulations of metformin are available. *Glucovance* is a combination of metformin and glyburide that may be helpful for diabetics who require both a sulfonylurea and metformin, and *Glucophage XR* is an extended-release product of metformin that may be better tolerated in some patients who are prone to gastrointestinal side effects. Metformin is usually given two to three times a day at mealtimes.

Thiazolidinediones

Thiazolidinediones (sometimes termed glitazones) are a novel class of drugs that were initially identified for their insulin-sensitizing properties. They all act to decrease insulin resistance and enhance insulin action in target tissues. Thiazolidinediones activate the nuclear peroxisome proliferator–activated receptor (PPAR) γ, a nuclear orphan receptor that is predominantly expressed in adipose tissue and to a lesser extent in muscle, liver, and other tissues. The endogenous ligand for the PPAR-γ receptor is postulated to be prostaglandin J2, and it appears to work by heterodimerizing with other nuclear receptors to modulate the expression of insulin-sensitive genes.

Thiazolidinediones are readily absorbed from the gastrointestinal tract following oral administration and are rapidly metabolized by the liver. Plasma elimination half-life is 2 to 3 hours for rosiglitazone (*Avandia*) and slightly longer for pioglitazone (*Actos*). About two-thirds of conjugated metabolites appear in the urine and the remainder in the feces. The biological effect of these drugs takes several weeks to develop, although patients may see some benefit within a few days to a week. Generally, however, the insulin-sensitizing action of the thiazolidinediones takes a while to develop. For that reason, upward adjustments in dosage are made gradually to avoid hypoglycemia.

The patient who would benefit the most from a thiazolidinedione is a type II diabetic with a substantial amount of insulin resistance (e.g., one who does not respond to other oral therapies or who requires excessive amounts of insulin [>100 units/day]). Improvements in diabetic control are variable, ranging from a 1% reduction in hemoglobin A1c when used as monotherapy to greater reductions (>2% reduction in hemoglobin A1c) when used in combinations with other agents, such as sulfonylureas or metformin.

Rosiglitazone is approved for use as monotherapy and in conjunction with metformin, though it is sometimes combined with a sulfonylurea or insulin. It is usually taken once or twice a day with or without food. Rosiglitazone may cause a modest increase in low-density lipoprotein and triglyceride concentrations, but it is unclear whether this effect has any clinical significance or persists in the long term.

Pioglitazone is approved for use as monotherapy and in conjunction with metformin, sulfonylureas, and insulin. It is taken once a day with or without food. Though pioglitazone may also cause a small increase in low-density lipoprotein concentrations, there is usually a modest decrease in triglyceride levels, but it unclear whether this has any clinical significance or persists in the long term.

The original prototype of this class of drugs, troglitazone (*Rezulin*), was taken off the U.S. market in 2000 because of increasing concerns about idiosyncratic hepatic toxicity that resulted in several deaths worldwide. Consequently, frequent monitoring of liver transaminases is recommended for rosiglitazone and pioglitazone, and these drugs should be stopped if transaminases rise to more than two to three times the upper limit of normal. To date, rosiglitazone and pioglitazone seem to be associated with far fewer incidents of hepatic toxicity.

Thiazolidinediones commonly cause edema that can be quite severe, sometimes requiring cessation of the drug, but mild cases of lower extremity edema can be treated with a low dose of a diuretic. There is often a modest amount of weight gain that is independent of water-retaining effects. In laboratory animals, thiazolidinediones at high doses are associated with ultrastructural histopathological changes in cardiac tissue; therefore, thiazolidinedione use is contraindicated in patients with significant heart failure. Thiazolidinediones can also cause mild anemia. Safety in pregnancy is not established.

Hypoglycemia is rare with thiazolidinedione monotherapy; however, these drugs may potentiate the hypoglycemic effects of concurrent sulfonylurea or insulin therapy. If a thiazolidinedione is to be added to a diabetic's regimen, the sulfonylurea or insulin dosage should be decreased to compensate for any enhanced insulin sensitivity. Occasionally a small portion of insulin-treated type II diabetics may be capable of coming off their insulin altogether, depending on their responsiveness to thiazolidinedione action.

α-Glucosidase Inhibitors

The α-glucosidase inhibitors primarily act to decrease postprandial hyperglycemia by *slowing the rate* at which carbohydrates are absorbed from the gastrointestinal tract. They act by competitively inhibiting α-glucosidases, a group of enzymes in the intestinal brush border epithelial cells that includes glycoamylase, sucrase, maltase, and dextranase. The prolongation of the intestinal absorption of carbohydrates results in a blunted insulin response, keeping postprandial hyperglycemia under control. To be effective, α-glucosidase inhibitors must be taken before or with meals. Theoretically, the α-glucosidase inhibitors are most beneficial in patients

with mild to moderate diabetes whose diet is more than 50% carbohydrates. α-Glucosidase inhibitors are not approved for used in type I diabetes.

Acarbose (*Precose*) is an oligosaccharide derivative that has a higher affinity for the α- glucosidase enzymes than do other dietary oligosaccharides. Systemic absorption of acarbose is very low (~2%), with most being broken down in the intestine to several metabolites. About half of the orally administered acarbose is excreted unchanged in the feces, while the remainder, some of which is systemically absorbed, is renally excreted. Acarbose may be associated with hepatotoxicity in rare instances.

Miglitol (*Glyset*) is another α-glucosidase inhibitor, but in contrast to acarbose, miglitol is systemically absorbed prior to its activity in the small intestine. It also appears to inhibit the enzymes sucrase and maltase to a greater extent than does acarbose. It does not undergo metabolism and is renally excreted unchanged.

Gastrointestinal disturbances (loose stools, flatulence, and abdominal cramping) are the most frequently observed side effects of the α-glucosidase inhibitors. These effects can be minimized by starting patients on a low dose and then slowly advancing the dose as tolerance develops; curtailment of carbohydrate consumption also can alleviate these effects. Patients should be counseled that these side effects will occur and that tolerance should develop; otherwise, compliance will be low and about one-third of patients will stop their medication. Unlike the sulfonylureas, insulin, and the thiazolidinediones, α-glucosidase inhibitors do not cause weight gain. Insulin levels do not change in the presence of α-glucosidase inhibitors, so fasting hypoglycemia does not occur when α-glucosidase inhibitors are used as monotherapy. Although the α-glucosidase inhibitors may be used as monotherapy, they are usually used in combination with metformin, sulfonylureas, or insulin. Under the best circumstances, α-glucosidase inhibitors can be expected to promote a 0.5 to 1% reduction in a patient's hemoglobin A1c. Leaving aside their gastrointestinal side effects, α-glucosidase inhibitors appear to be relatively safe.

Study Questions

1. The main reason metformin should not be used in patients with renal failure is that
(A) It increases the risk of lactic acidosis.
(B) It increases the risk of ketoacidosis.
(C) It causes development of congestive heart failure.
(D) It causes hepatic necrosis.
(E) It causes hypoglycemia.

2. All of the following statements are true EXCEPT
(A) Lispro insulin displays a similar affinity and action with the insulin receptor.
(B) Lispro insulin has a slower onset of action than glargine insulin.
(C) Premixed 70/30 insulin is composed of 70% NPH and 30% regular insulin.
(D) Glucagon is a hormone that counteracts many of the metabolic effects of insulin.
(E) Glargine insulin has a longer duration of action than lispro insulin.

3. Hypoglycemia is rarely seen with these drugs when used as monotherapy EXCEPT:
(A) Metformin
(B) Rosiglitazone
(C) Miglitol
(D) Glyburide
(E) A, B, and C

4. All of the following are true statements about the thiazolidinediones EXCEPT
(A) Thiazolidinediones may be hepatotoxic in some individuals.
(B) Thiazolidinediones increase the number of insulin receptors on the cell membrane surface.
(C) Thiazolidinediones bind a nuclear receptor in tissue termed PPAR-γ, which augments the expression of insulin-regulated genes.
(D) Thiazolidinediones take many days to weeks to begin exerting a blood glucose–lowering effect in diabetics.
(E) The most common side effects of thiazolidinediones are weight gain and edema.

ANSWERS

1. A. Metformin causes lactic acidosis in patients with renal failure and severe congestive heart failure. It does not increase the risk of ketoacidosis and showed a reduction in cardiovascular comorbidities in a large study. It is contraindicated in patients with severe liver disease but does not cause hepatic necrosis. When used as monotherapy, metformin rarely causes hypoglycemia.

2. B. Lispro insulin was engineered to have a rapid onset of action. Lispro insulin displays a similar affinity and action with the insulin receptor as regular insulin. Premixed 70/30 insulin is composed of a 70:30 ratio of NPH to regular insulin. Glucagon has opposite effects to many of those of insulin.

Glargine insulin has substituent groups that prevent deamidation and dimerization and that enhance its stability at physiological pH.

3. **D.** One of the most important therapeutic objectives is to maintain normal glucose levels without producing frequent hypoglycemia. The main class of hypoglycemic drugs that have a propensity to cause hypoglycemia are the sulfonylureas, of which glyburide is one. This is not a problem with the other choices.
4. **B.** The thiazolidinediones decrease insulin resistance and enhance insulin action in target tissues. The original prototype drug of this class was removed from the market because of hepatotoxicity. These compounds activate the PPAR-γ-receptor. Although patients may see some benefit within a few days, a clinically significant effect generally takes weeks. The most common side effects are edema and weight gain that is independent of the weight gain seen in edema.

SUPPLEMENTAL READING

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CASE Study Insulin Regimens

George Smith is taking insulin for the first time. His physician prescribes 20 units NPH and 5 units regular insulin at breakfast, and 10 units NPH and 5 units regular insulin at dinner. After a few days, Mr. Smith begins to notice this approximate pattern in his blood sugar measurements:

8 A.M. (fasting), about 110; noon (before lunch), about 120; 5 P.M. (before dinner), about 55; bedtime, about 115.

When his blood sugar is about 55, he feels shaky and sweaty, but this goes away if he has something to eat. Which of the following changes would you recommend to his regimen?

Decrease his morning regular insulin

Decrease his morning NPH insulin

Stop evening insulin and add a sulfonylurea at bedtime

Have him eat a larger lunch

Move his evening NPH insulin from supper time to bedtime

ANSWER: Mr. Smith should decrease his morning NPH insulin. Since on awakening his fasting glucose is in the normal range and after taking his morning regular insulin his blood glucose remains in the normal range, there is no need to adjust either his morning regular insulin or his bedtime NPH insulin. Regular insulin is short-acting and would not result in a 5 P.M. low glucose level. The longer-acting NPH insulin given in the morning would continue to lower glucose for the rest of the morning and afternoon, in this case resulting in excessive blood glucose at dinner time.