TEACHERS’ TOPICS

Insulin and Oral Antidiabetic Agents

Ahmed S. Mehanna, PhD

Massachusetts College of Pharmacy and Health Sciences
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The current manuscript describes an overview for therapeutic approaches to treat diabetes mellitus. Detailed presentation of the role of insulin in both disease state development and therapy is given. The article also addresses the classification, chemistry, pharmacokinetic properties, dosage forms, mechanisms of action, and therapeutic indications of oral anti-diabetic agents currently available for clinical use. The paper also details the rationale of differences in the onset and duration of action of various insulin preparations. The paper also briefly addresses the phenomena of development of insulin resistance, multi-ingredient dosage form of oral anti-diabetic agents, and approaches to teaching the topic in the classroom.

Keywords: insulin, anti-diabetic agents, hypoglycemic agents, diabetes

INTRODUCTION

Diabetes mellitus is a disorder characterized by hyperglycemia, altered metabolism of carbohydrates, lipids, and proteins. The disease’s clinical manifestations include hyperglycemia, glucosuria, polyuria, polydipsia, and the appearance of ketone bodies in breath and urine (ketonuria). These metabolic disturbances are predisposing factors for cardiovascular, hepatic, and renal complications. Severity of the disease complications closely correlates to glycosylated hemoglobin (HbA1c) levels, a parameter frequently employed as an index for monitoring the disease and for therapy prognosis. In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus developed a revision of the 1979 system for diabetes classification. The revised classification system is largely based on the etiology of the disease rather than on the pharmacological approach to managing it, which was the case with the 1979 system of classification. In the revised system, Arabic numbers rather than Roman numeral are used to describe the diabetes type and the terms insulin dependant and insulin non-dependent were eliminated. Type 1 diabetes is characterized by a state of absolute insulin deficiency resulting from the destruction of the pancreatic beta cells. This destruction is mediated by either autoimmune reactions (type-1A) or idiopathic factors (type-1B). Type 2 diabetes, on the other hand, is characterized by either a decrease in beta cell activity (insulin deficiency), insulin resistance (decrease in the peripheral glucose uptake), or an increase in hepatic glucose production. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus has also introduced several other specific types of diabetes related to genetic defects in the beta cell function and insulin action, diseases of the pancreas and other endocrine disorders, drug and chemical induced diabetes, infection-induced diabetes, and gastrointestinal diabetes mellitus.

Diabetes Management and Anti-Diabetic Drugs Classification

Approaches to managing diabetes depend on the disease state subtype. Due to the absence of endogenously synthesized hormone, type 1 diabetes requires insulin therapy from the start. Type 2 diabetes, on the other hand, can be managed with a variety of approaches including administration of insulin, stimulation of insulin release from the beta cells (sulfonylureas and metiglinides), increasing peripheral tissue utilization of glucose (insulin receptor sensitizers such as the thiazolidinediones), decreasing hepatic glucose production (the biguanides), and decreasing utilization of ingested carbohydrates (α-glycosidase inhibitors such as acarbose and miglitol). All currently available anti-diabetic agents lower blood glucose levels by one or more of the above listed mechanisms.

Management of both type 1 and type 2 diabetes aims primarily at normalizing blood glucose levels to prevent short- and long-term complications. Below is a detailed description of chemical structures, kinetic properties, the mechanisms of action, dosage forms, and therapeutic indications for insulin and oral anti-diabetic
drug classes and their place in therapy. Special emphasis is given to insulin due to its role in both therapy and disease pathogenesis.

**Insulin.** **Chemistry and biosynthesis.** Insulin is a protein with about 6000 molecular weight, produced by the beta cells of the pancreas. The hormone is chemically composed of 2 polypeptide chains designated as chain “A,” comprised of 21 amino acids, and chain “B,” comprised of 30 amino acids. The 2 chains are connected through 2 intermolecular disulfide bridges. Figure 1 depicts the structure of human insulin. Insulin derived from animal sources differs from human insulin in 1 or more of the amino acids. Pork insulin differs from human insulin in 1 amino acid at position 30 of the B-chain (B30), where alanine replaces threonine. The interspecies structural differences of insulin products do not significantly affect the biological activities; however, the antigenic properties increase with the number of amino acids changes. In all species, insulin is biosynthesized in the pancreas as a precursor form (proinsulin) of continuous single peptide chain in which the carboxyl-terminal of chain A (A30), and the amino-terminal of chain B (B1) are connected through a 35 amino acid chain C. Proinsulin is stored in the pancreas as a complex with zinc ions. At times when insulin is physiologically needed, chain C cleaves off by certain proteolytic enzymes to produce the active form of insulin shown in Figure 1.

**Distribution.** Once insulin is released from the pancreas it is rapidly distributed throughout the extracellular fluids, with no plasma protein binding.

**Metabolism.** Insulin metabolism occurs mainly in the liver and, to a much lesser extent, in the kidneys and muscle tissues. The enzyme insulin-glutathione transhydrogenase cleaves the intermolecular disulfide bonds holding the A and B chains. Insulin has a short half-life (about 5-6 minutes), and 50% of circulating insulin is deactivated by the liver with each cycle.

**Excretion.** Unmetabolized insulin is filtered through the kidney’s glomeruli and almost completely (98%) reabsorbed in the proximal tubules back into circulation for further actions and/or metabolism. In normal patients, only 2% of the filtered dose is excreted unchanged in urine. Renal impairment greatly affects the rate of insulin disappearance from circulation.

**Actions and mechanism of action.** Insulin facilitates glucose entry into adipose tissues, muscles, and liver by stimulating several enzymatic reactions that start at the insulin receptors. The stimulation of an intrinsic tyrosine kinase of the insulin receptor results in an increase in membrane phosphorylation that consequently increases the membrane permeability to glucose through a complicated cascade of intracellular events.

**Insulin resistance.** Insulin resistance underlies potentially adverse metabolic changes, such as the concentrations of insulin, glucose, lipoproteins, lipids, blood pressure, and other cardiovascular diseases. Resistance to insulin therapy develops in both types of diabetes; however, it is infrequent with type 1 and if it occurs, resistance can be induced by either immune or nonimmune factors. Insulin resistance in patients with type 2 diabetes is more frequent and associated mainly with obesity. The resistance to insulin is simply tissue insensitivity hormone manifested as either a decrease in the number of insulin receptors or a decrease in insulin affinity to its receptors. Insulin resistance is further classified as either acute or chronic resistance. While acute resistance develops in patients exposed to infections, surgical trauma, or emotional disturbances, chronic resistance is immunological in nature and results from the formation of antibodies to insulin. Resistance occurs mostly with patients who have insulin therapy reinstated after a period of withdrawal.

**Pharmaceutical insulin preparations.** Routes of administration. Injection is the most widely recognized...
route for insulin administration. Although the peptide nature of insulin explains the preclusion of its oral use, several oral insulin preparations are under clinical trials to assess efficacy in providing glycemic control for diabetic patients. Inhalation insulin has been introduced in a single-blind, placebo-controlled, nonrandomized preliminary study as another approach to delivering insulin. The study revealed promising effects; however, significant questions regarding the reproducibility in multiple-dose studies and the potential toxicity of inhaled insulin to lungs must be answered before inhalation insulin becomes available for widespread use. In addition to attempts to administer insulin orally and by inhalation, several other new routes for delivery are still under investigation, including intraperitoneal delivery devices, implantable pellets, closed-loop artificial pancreas, gene therapy, and islet cells and pancreatic transplantation.

At present, insulin is commercially available for subcutaneous, intravenous, and intramuscular use. Insulin preparations have evolved from those produced from animal species to human insulin preparations produced with recombinant DNA technology. Although animal and human insulin preparations do not significantly differ in activities, increased risk in causing allergic reaction poses a concern. At present, insulin preparations derived from animals are limited to those produced from pork (porcine). Insulin products are classified as rapid, intermediate, or long acting according to their onset and duration of action. The onset and duration of action of insulin products directly relate to the preparation’s zinc content. Products containing a low amount of zinc, such as regular insulin, generally act faster and have a short duration of action, while those containing a high amount of zinc, such as ultralente insulin, have a slower onset but long duration of action. Combination insulin products are commercially available to provide both the benefits of fast onset and long duration of action.

### Rapid-acting insulin preparations

Insulin products intended to provide rapid action are prepared in either water for injection or in a phosphate buffer solution containing minute amounts of zinc chloride (0.01-0.04 mg/100U). Rapid-acting insulin preparations include regular, lispro, insulin aspart, and glulisine insulins. Each is described below, along with the chemical features of each product. Table 1 provides the generic and trade names, onset, duration of action, and available dosage forms for each preparation.

#### Regular insulin

Regular insulin is a solution of insulin in either water for injection or phosphate buffer containing minute amounts of zinc chloride (0.01-0.04 mg/100U). Zinc ions form complexes with insulin and allow the formation of insulin hexamer. At the site of injection, the hexamer dissociates into dimers and further to monomers that rapidly diffuse into circulation and give the rapid onset of action (30 minutes).

#### Insulin lispro

Insulin lispro is the first human insulin analog produced by recombinant DNA technology through site-directed mutation. Lispro insulin has the amino acids 28 and 29 of the B chain switched to become lys-pro (hence the name lispro) instead of the pro-lys configuration present in regular human insulin. Insulin lispro differs from regular insulin by virtue of its capacity to dissociate faster into dimers and further to monomers that rapidly diffuse into circulation and give the rapid onset of action (30 minutes).

#### Insulin aspart

Insulin aspart is another rapid-acting human insulin analog produced by recombinant DNA technology through site-directed mutation. Aspart insulin has the amino acids 28 and 29 of the B chain switched to become lys-pro instead of the pro-lys configuration present in regular human insulin. Insulin aspart has a faster onset of action than regular insulin (15 minutes).
acid (hence the name aspart). At physiological pH, aspartic acid renders the insulin surface negatively charged, which in turn results in a faster dissolution rate from the injection site and faster onset of action (15 minutes).

**Insulin glulisine.** Glulisine is the newest of insulin analog and differs from human insulin in the replacement of the B3 amino acid asparagine with lysine and the B29 lysine with glutamic acid (hence the name glulisine). The product has identical properties to insulin aspart with an onset of action of 20 minutes.

**Intermediate-acting insulin preparations.**

- **Neutral Protamine Hagedorn.** Neutral Protamine Hagedorn (NPH) is prepared in phosphate buffer as a white suspension containing insulin, protamine (a very basic protein), and 0.016-0.04 mg zinc/100 Units. The combination of insulin, protamine, and zinc forms a complex product with reduced solubility, and consequently a slower dissolution rate from the site of injection. NPH has 1- to 2-hour onset of action and 18-24 hours duration of action.

- **Lente insulin.** Lente insulin is another insulin preparation with intermediate duration of action. The product is a mixture of 2 types of insulin particles, amorphous and crystalline. The formation of an insulin-zinc complex under low zinc concentrations (0.016-0.04 mg zinc/100 Units) produces the amorphous particles (semilente insulin), which have rapid onset of action due to the large surface area of dissolution. Semilente insulin is no longer available in the United States as a separate preparation due to the development of other faster-acting products. On the other hand, the formation of an insulin-zinc complex in a high zinc concentration (0.2-0.25 mg zinc/100 Units) produces large crystalline particles (ultralente insulin). The limited surface area of such particles results in a slower dissolution rate at the site of injection and an accordingly longer duration of action. Lente insulin is a mixture of semilente and ultralente insulin products. The preparation is a white suspension prepared in an acetate buffer and contains 0.2-0.25 mg zinc/100 Units. The kinetic properties of lente insulin are similar to those of NPH insulin. Table 2 summarizes different properties of the intermediate-acting insulin preparations.

**Long-acting insulin preparations.**

- **Ultralente insulin.** The product is prepared as described above by allowing insulin to form a complex with high zinc concentration in acetate buffer. The product has a zinc content of 0.2-0.25 mg/100 Units, a 4- to 6-hour onset of action, and a duration of action of 20-36 hours.

- **Glargine insulin.** Glargine insulin is the first long-acting human insulin analog to be developed by recombinant DNA technology. The product has multimutation sites in both the A and B chains of human insulin. Chain A has the amino acid at position A21 (asparagine) replaced with glycine, while chain B has additional 2 arginine residues added to the C-terminus. These modifications stabilize the insulin hexamer and result in a slower dissociation rate and delayed release from the site of injection. The preparation has a low zinc content of 0.03 mg/100 Units, a 2- to 5-hour onset of action, and a duration of action of 18-24 hours. Table 3 summarizes the properties of ultralente and glargine insulin preparations.

**Premixed insulin preparations.** Several premixed insulin preparations are formulated to provide both rapid and delayed insulin effects. NPH insulin is a common denominator in these preparations to provide the prolonged effects. It is mixed with one of the fast-acting products such as regular insulin, lispro insulin, or insulin aspart in various percentages ranging from 10% to 50% to provide immediate effects. Table 4 lists premixed insulin preparations.

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**Table 2. Intermediate-acting Insulin Preparations**

<table>
<thead>
<tr>
<th>Insulin Product</th>
<th>Source</th>
<th>Trade Name(s)</th>
<th>Onset of Action (hrs)</th>
<th>Duration of Action (hrs)</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isophane Insulin Pork</td>
<td>Pork</td>
<td>Iletin II NPH Purified Pork</td>
<td>3-4</td>
<td>18-24</td>
<td>100 Units/ml as suspension in phosphate buffer</td>
</tr>
<tr>
<td></td>
<td>Pork</td>
<td>Insulin NPH Purified Pork</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isophane Insulin</td>
<td>Recombinant DNA</td>
<td>Humulin N</td>
<td>1-3</td>
<td>18-24</td>
<td>100 Units/ml as suspension in acetate buffer</td>
</tr>
<tr>
<td>Human</td>
<td>DNA</td>
<td>Humulin N Pen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNA</td>
<td>Novolin N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Zinc</td>
<td>Pork</td>
<td>Iletin II Lente Purified Pork</td>
<td>3-4</td>
<td>18-24</td>
<td>100 Units/ml as suspension in phosphate buffer</td>
</tr>
<tr>
<td></td>
<td>Pork</td>
<td>Insulin Lente Purified Pork</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Human Zinc</td>
<td>Recombinant DNA</td>
<td>Humulin L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNA</td>
<td>Novolin Ge Lente</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NPH = Neutral Protamine Hagedorn
preparations that are currently available in the United States.

**Therapeutic indications of insulin.** Insulin is the primary treatment for patients with type 1 diabetes. For patients with type 2 diabetes, insulin therapy is initiated only when diet or oral antidiabetic agents fail to control the blood glucose levels, and in cases of postpancreatectomy. Insulin, especially rapid-acting preparations, are critical for the management of diabetic ketoacidosis, prevention of hyperglycemic nonketonic coma, and perioperative management of both type 1 and type 2 patients.

**Oral Anti-Diabetic Agents**

Oral anti-diabetic drugs include sulfonylureas, non-sulfonylurea secretagogues, biguanides, insulin receptor enhancers (sensitizers), and α-glucosidase inhibitors. Members of each class are used individually or in combination to manage patients with type 2 diabetes.\(^7\)-\(^9\)

**Sulfonylureas. Chemistry and classification.** All members of the class have 2 basic chemical entities: an acidic functional group (sulfonylurea), a substituted aromatic ring, and an alkyl group with 3-7 carbons on the urea nitrogen. Sulfonylureas are classified as either first- or second-generation drugs. The 2 subclasses differ in the size of the lipophilic group of the aromatic ring. Second-generation members have more lipophilic groups than those of the first generation. First-generation sulfonylurea drugs include tolbutamide, tolazamide, acetohexamide, and chloropropamide, and second-generation drugs include glyburide, glipizide, and glimepiride. Figure 2 illustrates the general formula of sulfonylureas, names, and substitution groups for commercially available first- and second-generation drugs.

**Pharmacokinetic properties.** Most members of the class share similar kinetic properties for absorption, distribution, metabolism, and excretion (ADME). Absorption after oral administration is generally rapid and complete. Sulfonylureas have strong plasma protein binding due to their lipophilic and acidic nature. Metabolism is mainly by the liver. Second-generation sulfonylureas undergo the entero-hepatic circulation recycling, a process that contributes to the long duration of action observed for all members of the subclass.

**First-generation sulfonylureas. Tolbutamide and tolazamide.** Tolbutamide and tolazamide are short-acting sulfonylureas due to the fast metabolic oxidation of the

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**Table 3. Long-acting Insulin Preparations**

<table>
<thead>
<tr>
<th>Insulin Product</th>
<th>Source</th>
<th>Trade Name(s)</th>
<th>Onset of Action (hrs)</th>
<th>Duration of Action (hrs)</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended insulin human zinc suspension</td>
<td>DNA</td>
<td>Humulin U Novolin ge Ultralente</td>
<td>4-6</td>
<td>20-36</td>
<td>100 Units/ml as suspension in acetate buffer</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Recombinant</td>
<td>Lantus</td>
<td>2-5</td>
<td>18-24</td>
<td>100 Units/ml as clear solution in 85% aqueous glycerol solution</td>
</tr>
</tbody>
</table>

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**Table 4. Premixed Insulin Preparations**

<table>
<thead>
<tr>
<th>Insulin Product</th>
<th>Source</th>
<th>Composition</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humulin 10/90</td>
<td>Recombinant</td>
<td>10% insulin human injection 100 Units/ml as suspension in phosphate buffer</td>
<td></td>
</tr>
<tr>
<td>Novolin 10/90 ge PenFill</td>
<td>DNA</td>
<td>+ 90% isophane suspension</td>
<td>phosphate buffer</td>
</tr>
<tr>
<td>Humulin 20/80</td>
<td>Recombinant</td>
<td>20% insulin human injection 100 Units/ml as suspension in phosphate buffer</td>
<td></td>
</tr>
<tr>
<td>Novolin 20/80 ge PenFill</td>
<td>DNA</td>
<td>+ 80% isophane suspension</td>
<td>phosphate buffer</td>
</tr>
<tr>
<td>Humulin 70/30</td>
<td>Recombinant</td>
<td>70% isophane suspension</td>
<td>phosphate buffer</td>
</tr>
<tr>
<td>Novolin 70/30 ge PenFill</td>
<td>DNA</td>
<td>+ 30% insulin human injection 100 Units/ml as suspension in phosphate buffer</td>
<td></td>
</tr>
<tr>
<td>Humulin 40/60</td>
<td>Recombinant</td>
<td>40% insulin human injection 100 Units/ml as suspension in phosphate buffer</td>
<td></td>
</tr>
<tr>
<td>Novolin 40/60 ge PenFill</td>
<td>DNA</td>
<td>+ 80% isophane suspension</td>
<td>phosphate buffer</td>
</tr>
<tr>
<td>Humulin 50/50</td>
<td>Recombinant</td>
<td>50% isophane suspension</td>
<td>phosphate buffer</td>
</tr>
<tr>
<td>Novolin ye 50/50 PenFill</td>
<td>DNA</td>
<td>+ 50% insulin human injection 100 Units/ml as suspension in phosphate buffer</td>
<td></td>
</tr>
<tr>
<td>Insulin-lispro protamine</td>
<td>Recombinant</td>
<td>75% NPH suspension 100 Units/ml as suspension in phosphate buffer</td>
<td></td>
</tr>
<tr>
<td>Protamine crystalline aspart 70/30</td>
<td>Recombinant</td>
<td>70% NPH suspension 100 Units/ml as suspension in phosphate buffer</td>
<td></td>
</tr>
</tbody>
</table>
aromatic ring methyl groups (Figure 2) into the inactive carboxylic acid metabolites. These drugs require multiple daily administrations.

**Acetohexamide.** The drug differs from tolbutamide and tolazamide in the activity of its metabolite that has acetyl-carbonyl group (Figure 2) reduced in the liver into the corresponding secondary alcohol. The drug is generally administered twice a day.

**Chloropropamide.** The presence of the chlorine atom at position 4 of the drug benzene ring (Figure 2) decreases metabolic deactivation at this position and renders the drug to be the longest-acting first-generation sulfonylurea and suitable for once a day administration. In addition to resistance of metabolism, the drug undergoes recycling through the entero-hepatic circulation that may further contribute to its long duration of action.

**Second-generation sulfonylureas.** As stated earlier, all members of the second-generation class of sulfonylureas share the presence of a large lipophilic group at the aromatic ring. Second-generation drugs are about 50- to 100-fold more potent than first-generation drugs and generally are longer acting.

**Glyburide, glipizide, and glimepride.** Glyburide, glipizide, and glimepride are representative examples of the class, and all administered once a day. Chemical structures of both first- and second-generation sulfonylurea drugs are depicted in Figure 2, and their properties are summarized in Table 5.

**Mechanism of action.** Sulfonylureas lower blood glucose levels by stimulating insulin release from the beta cells of the pancreas. The biochemical mechanism of action involves blocking the ATP-sensitive potassium channels. The latter leads to membrane depolarization and to an increase in calcium influx that in turn triggers the release of insulin from the beta islets. The effect of sulfonylureas on the membrane-potassium conductance resembles that of the physiological secretagogues (insulin release stimulators) such as glucose and amino acids. Sulfonylureas also have more complex effects on insulin blood levels by reducing insulin-hepatic clearance. Prolonged use of sulfonylureas may result in developing periodic episodes of hypoglycemia, a phenomenon generally described as hyperinsulinemia. Sulfonylureas are indicated only for the treatment of type 2 diabetes and they are not appropriate to treat type 1 diabetes.
The Metiglinides. (Non-Sulfonylurea Secretagogues)\(^\text{26}\) Knowledge that sulfonylureas act as insulin secretagogues through blocking the potassium channels prompted the idea of testing more selective potassium channel blockers for anti-diabetic activities. The metiglinide family of oral anti-diabetic agents acts purely by such mechanism and its members are generally described as the non-sulfonylurea secretagogues. The metiglinides are carboxylic acid derivatives (benzoic or phenylacetic); characterized by being 5-10 times more potent than sulfonylurea drugs, having faster onset but shorter duration of actions, and show no hyperinsulinemia.

Repaglinide and nateglinide. These 2 agents are representative examples of this class. Figure 3 depicts the chemical structures of the 2 drugs, and their properties are listed in Table 6. Like the sulfonylureas, the metiglinides are not appropriate to treat type 1 patients and are useful only for the treatment of type 2 diabetes.

Biguanide. Biguanides\(^\text{27,28}\) are basic molecules due to the biguanide groups. The biguanides do not induce the release of insulin from the pancreas so they are not classified as secretagogues. Drugs in this class reduce blood glucose levels primarily by either decreasing hepatic glucose production, through inhibiting gluconeogenesis and glycogenolysis, or by stimulating glucose peripheral breakdown through stimulating anerobic glycolysis. The biguanides do not lower normal blood glucose levels so they are not hypoglycemic agents, rather they act only on elevated blood glucose levels, so they are classified as antihyperglycemic agents. Members of the class include metformin, phenformin, and buformin. Clinical use of these drugs is associated with high incidences of lactic acidosis, which sometimes can be fatal. Phenformin is the worse in that regard, accordingly it was withdrawn from the United States market.

Metformin. Metformin is the most commonly used member of the biguanide series with no reports of lactic acidosis. The drug’s parent nucleus is a condensation product of 2 guanidine groups (hence the name biguanides) that imparts basic and polar characteristics (poor bioavailability after oral administration). Metformin is administered 2-3 times and it is absorbed mainly from the small intestine with no plasma protein binding, it undergoes minimal metabolism, and is excreted mostly unchanged in urine. The drug is contraindicated in patients with hepatic or renal diseases, and must be discontinued if lactic acid plasma levels reach 3 mM or above. Figure 4 depicts the chemical structures of the 3 drugs, and Table 7 lists metformin’s properties.

Insulin Sensitizers. Insulin sensitizers (the thiazolidinediones)\(^\text{29-31}\) do not have hypoglycemic nor antihyperglycemic affects if administered alone. However, when co-administered with insulin, the required insulin dose can be reduced by half, hence the term insulin sensitizers. Members of the class are useful in managing cases of diabetes when insulin resistance exists. Insulin sensitizers are derivatives of thiazolidindione nucleus, substituted at position 5 with a benzyl group, which is in turn further substituted at position 4’ with various lipophilic moieties (Figure 5). The first developed drug of this class was

![Figure 3. Non-sulfonylurea secretagogues.](image-url)
troglitazone, which was withdrawn later from the United States market due to reports of severe liver toxicity.

**Rosiglitazone and pioglitazone.** Rosiglitazone and pioglitazone are members of the thiozolidinedione class and still in clinical use in the United States, with no reports of liver toxicity. Figure 5 depicts the chemical structures of the two drugs, and Table 8 summarizes its properties. The drugs act through activation of insulin responsive genes in the nucleus that regulate lipid and carbohydrate metabolism. Gene activation occurs through selective agonistic action of the drugs on the nuclear receptors called \textit{peroxisome proliferator-activated receptor-gamma} (PPAR\textsubscript{\textgamma}).\textsuperscript{30,31} Insulin sensitizers administered in combination with insulin and oral anti-diabetic agents for cases of insulin resistance diabetes.

**Alpha-glucosidase Inhibitors.** Alpha-glucosidase inhibitors\textsuperscript{32,33} belong to the class \(\alpha\)-glucosidase inhibitors act mainly to delay and decrease the absorption of complex carbohydrates from the gastrointestinal tract. Under normal conditions, the enzyme \(\alpha\)-glucosidase generates glucose in the gastrointestinal tract by hydrolyzing the dietary oligosaccharides such as starch, dextrin, and maltose. Inhibition of the enzyme decreases the amounts of glucose available for absorption from the gastrointestinal tract.

**Acarbose and miglitol.** Acarbose\textsuperscript{32} and miglitol\textsuperscript{33} represent this class of drugs and were approved for use in the United States. Acarbose is a carbohydrate-like polymer structure, while miglitol is a polyhydroxylated cycloheane derivative. The polar nature of these drugs precludes absorption after oral administration, and ensures high concentration in the gastrointestinal tract, where the drugs are designed to act. Figure 6 depicts the chemical structures of acarbose and miglitol, and Table 9 summarizes its properties. Drugs belonging to this class are considered to be safe the and used as either adjunct therapy with other agents or as mono therapy for elderly patients.\textsuperscript{34}

### Multi-Ingredient Dosage Forms of Oral Anti-Diabetic Agents

If diet fails to control the disease, an oral antidiabetic agent is introduced to the therapy of type 2 diabetic patients to normalize blood glucose levels. In several cases, optimum control of glucose levels requires concurrent use of 2 of these agents, such as metformin with glyburide, glipizide, or rosiglitazone. Multi-oral therapy aims to include 2 agents that work through different mechanisms. For example, while metformin acts to decrease hepatic glucose output, a sulfonylurea drug acts to stimulate insulin release from the pancreas, or rosiglitazone acts to increase the peripheral utilization of glucose. Several pharmaceutical dosage forms are currently available containing premixed oral antidiabetic agents in a single tablet. Among these products: glucovance (metformin + glyburide), metaglip (metformin + glipizide), and Avandamet (metformin + rosiglitazone). In addition to the therapeutic benefits, these multi-ingredient tablets are also convenient for patients since they reduce the number of tablets the patient has to take with each meal. Table 10 lists the composition of each of these multi-ingredient products.

### Place of Insulin and Oral Anti-Diabetic Agents

#### Diabetes Therapy

As previously indicated, the primary treatment for type 1 diabetes is insulin to maintain strict glycemic control and prevent and delay disease complications. Intensive
insulin therapy often involves 3 or more injections daily or use of an insulin pump. Although insulin is available as a single product preparation as fast/short-acting (regular insulin, insulin lispro, insulin aspart, insulin glulisine), delayed/intermediate acting (neutral protamine insulin (NPH), lente insulin), or delayed/long-acting (ultra-lente, insulin glargine), premixed formulations of more than 1 type of insulin are available to provide both fast- and long-acting effects. The dose of insulin depends on the individual’s glycemic response to food intake as well as exercise. Rapid-acting insulin preparations such as lispro, aspart, or glulisine should be administered shortly before meals; and regular insulin should be administered 30 minutes before meals. An intermediate, or long-acting insulin may be required to maintain glycemic control during the day. The addition of insulin to oral hypoglycemic therapy for the treatment of type 2 diabetes has been shown to enhance glycemic control, especially in patients in whom combination oral therapy has failed and those who have developed resistance to insulin. As type 2 diabetes progresses, insulin serum levels become insufficient to compensate for insulin resistance. Supple-

Classroom Teaching of Anti-Diabetic Drugs

The material presented above on insulin and oral anti-diabetic agents is taught over three 50-minutes lectures in the second semester Medicinal Chemistry II course (CHE442). The course is a required 3-credit course offered during the spring semester of the fourth-year curriculum for the 6-year doctor of pharmacy program (Pharm D) at the Massachusetts College of Pharmacy and Health Sciences. Presentation of the material was closely coordinated with the Pharmacology course (PHL452), which covers the same topic in the same week. The presentation is largely in a lecture-based format supported with handouts illustrating the classification and chemical structures of different drugs. The pace of the presentation was set to allow students to take comprehensive and detailed notes during class. In addition, questions and comments were encouraged at any point of the presentation. The presented basic science information about insulin and antidiabetic medications were always linked to clinical applications with emphases on the role of the PharmD in counseling patients about these medications.

Table 9. Alpha-Glucosidase Inhibitors

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Names</th>
<th>Tablet Strength (mg)</th>
<th>Frequency of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>Avandia</td>
<td>4.0</td>
<td>once daily</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Actors</td>
<td>15; 30; 45</td>
<td>once daily</td>
</tr>
</tbody>
</table>

Figure 6. Alpha-glucosidase inhibitors.

Table 10. Oral Anti-diabetic Multi-ingredient Formulations

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Composition</th>
<th>Tablet Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucovance</td>
<td>metformin + glyburide</td>
<td>500 mg metformin + 1.25; 2.5; or 5 mg glyburide</td>
</tr>
<tr>
<td>Metaglip</td>
<td>metformin + glipizide</td>
<td>250 mg metformin + 2.5 mg glipizide; 500 mg metformin + 2.5 mg glipizide</td>
</tr>
<tr>
<td>Avandamet</td>
<td>metformin + rosiglitazone</td>
<td>500 mg metformin + 1, 2, or 4 mg rosiglitazone</td>
</tr>
</tbody>
</table>
Examinations are always in multiple-choice format due to the large class size (232 students). The students’ responses to questions pertaining to the diabetes lectures were always at the 90% response range or above. Furthermore, the students’ evaluations at the end of the course reflect great appreciation for the efforts made toward linking the basic information to the clinical practice.

**SUMMARY**

Insulin and oral antidiabetic agents are available tools for managing the disease state of diabetes mellitus. Insulin pharmaceutical preparations are classified based on the onset and duration of action into rapid, intermediate, and long-acting preparations. Insulin is effective in the treatment of both type 1 and type 2 diabetes. Resistance to insulin therapy may develop with prolonged use in both types of diabetes. Five classes of oral antidiabetic agents are currently available for clinical use. The drug classes include: sulfonylureas, non-sulfonylurea secretagogues (the thiazolidinediones), biguanides, insulin receptors sensitizers, and α-glucosidase inhibitors. Each of the above classes has different kinetic properties, mechanism of action, dosage forms, and therapeutic indications.

**REFERENCES**


