Chapter-6

DRUGS PROFILE
REPAGLINIDE

Molecular formula: C_{27}H_{36}O_{4}N_{2}

Molecular weight: 452.59

Description:

Repaglinide (Prandin) is an oral insulin secretagogue of the meglitinide class. This agent is a derivative of benzoic acid & chemically it is: (S)-2-ethoxy-4-{2-[3-methyl-1-[2-(1-piperidinyl) phenyl] butyl amino]-2-oxoethyl} benzoic acid.

![Structure of Repaglinide](image)

**Clinical Pharmacology:**

*Mechanism of action:*

It is the first member of a new class of oral hypoglycemic designed to normalize the mealtime glucose excursions. Though not a sulfonylurea, it acts in an analogous manner by binding to sulfonylurea as well as to other distinct receptors — closer of ATP dependent K⁺ channels — depolarization — insulin release.

Repaglinide induces rapid onset short lasting insulin release. It is administered
before each major meal to control postprandial hyperglycaemia; the dose may be
omitted
if a meal is missed. Because of short lasting action it may have a lower risk of serious
Hypoglycemia. Side effects are mild headache, dyspepsia, arthralgia, and weight gain.

Repaglinide is indicated only in type II DM as an alternative to sulfonylurea, or to
Supplement metformin/long acting insulin. It should be avoided in the liver disease.

**Pharmacokinetic data of Repaglinide:**

After oral administration, Repaglinide is rapidly and completely absorbed
from the gastrointestinal tract. After single and multiple oral doses in healthy
subjects or in
Patients, peak plasma drug levels (Cmax) occurs within 1 hour (Tmax). Repaglinide is
rapidly eliminated from the blood stream with a half life of approximately 1-hour. The
mean absolute bioavailability is 56%. When Repaglinide was given with food.

Repaglinide is 98% bound to plasma proteins, primarily to albumin. The drug
is
Completely metabolized by oxidative biotransformation and direct conjugation with
Glucuronic acid after either an intravenous or oral dose. Metabolites do not contribute
to the glucose-lowering effect of Repaglinide.

Table 7: Pharmacokinetic data of Repaglinide
<table>
<thead>
<tr>
<th>S.NO</th>
<th>Drug</th>
<th>Repaglinide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Elimination half life($t_{1/2}$)</td>
<td>1hr</td>
</tr>
<tr>
<td>2.</td>
<td>Duration of action</td>
<td>2-3</td>
</tr>
<tr>
<td>3.</td>
<td>Clearance route</td>
<td>Liver</td>
</tr>
<tr>
<td>4.</td>
<td>Daily dose</td>
<td>1.5-8mg</td>
</tr>
<tr>
<td>5.</td>
<td>Number of doses per day</td>
<td>3-4 per day</td>
</tr>
<tr>
<td>6.</td>
<td>Elimination rate constant($K_e$)</td>
<td>0.693hrs</td>
</tr>
<tr>
<td>7.</td>
<td>Peak plasma level($C_{max}$)</td>
<td>37.5mg/mL</td>
</tr>
<tr>
<td>8.</td>
<td>Apparent volume of distribution</td>
<td>31.0L</td>
</tr>
<tr>
<td>9.</td>
<td>Therapeutic concentration range</td>
<td>0.5-4mg</td>
</tr>
<tr>
<td>10.</td>
<td>Bio availability</td>
<td>56%</td>
</tr>
</tbody>
</table>

**Indications:**

Repaglinide is indicated as an adjunct to diet and exercise to lower the blood glucose levels in patients with type II diabetes mellitus (NIDDM) whose hyperglycaemia cannot be controlled satisfactorily by diet and exercise alone.

Rapaglinide is also indicated for use in combination with metformin to lower blood glucose levels in patients whose hyperglycaemia cannot be controlled satisfactorily by diet, exercise and either Repaglinide or metformin alone.

**Drug interactions:**
Invitro data indicate that antifungal agents like ketoconazole and miconazole may inhibit Repaglinide metabolism, and antibacterial agents like erythromycin. Drugs that induce the cytochrome P-450 enzyme system 3A4 may increase Repaglinide metabolism; such drugs include troglitazone, rifampin, barbiturates, and carbamazepine.

Repaglinide had no clinically relevant effect on the pharmacokinetics properties of digoxin, theophylline, or warfarin.. Thus no dosage adjustment is required for digoxin, theophylline, or warfarin on co-administration of cimetidine with Repaglinide did not significantly alter the absorption and disposition of Repaglinide.

**Side effects:**

In various clinical trials, the most common side effects leading to withdrawal were hyperglycaemia, hypoglycaemia and related symptoms. Other commonly reportedly side effects were upper respiratory tract infections, nausea, vomiting, arthralgia, backpain and headache. The incidence of serious cardiovascular side effects added together, including ischaemia was slightly higher for Repaglinide (4 %) than for sulfonylurea drug (3 %) in controlled comparator clinical trials

**Overdosage:**

There were few adverse effects other those associated with the intended effect of lowering blood glucose in the patients who received increasing doses of Repaglinide upto 80 mg a day for 14 days. Hypoglycaemia did not occur when meals were given with these high doses. Hypoglycaemia symptoms without loss of consciousness or
neurologic findings should be treated aggressively with oral glucose and adjustment in drug dosage.

**Dosage and Administration:**

There is no fixed-dosage regimen for the management of type II diabetes with Repaglinide. Short-term duration of Repaglinide may be sufficient during periods of transient loss of control in patient’s usually well-controlled on diet. Repaglinide doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

**Starting dose:**

For patients not previously treated or whose glycosylated haemoglobin is < 8% the starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drug and whose glycosylated haemoglobin is < 8% the initial dose is 1 or 2 mg with each meal pre-prandial.

**Dose adjustment:**

Dosage adjustment should be determined by blood glucose response, usually fasting blood glucose. The pre-prandial dose should be doubled up to 4 mg with each meal until satisfactory blood glucose response is achieved. At least one week should elapse to assess response after each dose adjustment.

**Insulin**
Insulin is a hormone central to regulating carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle.

Insulin stops the use of fat as an energy source by inhibiting the release of glucagon. With the exception of the metabolic disorder diabetes mellitus and Metabolic syndrome, insulin is provided within the body in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic. When blood glucose levels fall below a certain level the body begins to use fat as an energy source or gluconeogenesis; for example, by transfer of lipids from adipose tissue to the liver for mobilization as an energy source. As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). In addition, it has several other anabolic effects throughout the body.

When control of insulin levels fails, diabetes mellitus will result. As a consequence, insulin is used medically to treat some forms of diabetes mellitus. Patients with type 1 diabetes depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with type 2 diabetes are often insulin resistant, and because of such resistance, may suffer from a "relative" insulin deficiency. Some patients with type 2 diabetes may eventually require insulin if other medications fail to control blood glucose levels adequately. Over 40% of those with Type 2 diabetes require insulin as part of their diabetes management plan.

Insulin also influences other body functions, such as vascular compliance and cognition. Once insulin enters the human brain, it enhances learning...
and memory and benefits verbal memory in particular.\textsuperscript{[2]} Enhancing brain insulin signaling by means of intranasal insulin administration also enhances the acute thermoregulatory and glucoregulatory response to food intake, suggesting central nervous insulin contributes to the control of whole-body energy homeostasis in humans.

Fig 7: Structure of insulin

Insulin is a peptide hormone composed of 51 amino acids and has a molecular weight of 5808 Da. It is produced in the islets of Langerhans in the pancreas. The name comes from the Latin \textit{insula} for "island". Insulin's structure varies slightly between species of animals. Insulin from animal sources differs somewhat in "strength" (in carbohydrate metabolism control effects) in humans because of those variations. Porcine insulin is especially close to the human version.

Within vertebrates, the amino acid sequence of insulin is extremely well preserved. Bovine insulin differs from human in only three amino acid residues, and porcine insulin in one. Even insulin from some species of fish is similar enough to human to be clinically effective in humans. Insulin in some invertebrates is quite similar in sequence to human insulin, and has similar physiological effects. The strong homology seen in the insulin sequence of diverse species suggests it has been
conserved across much of animal evolutionary history. The C-peptide of proinsulin (discussed later), however, differs much more amongst species; it is also a hormone, but a secondary one.

The primary structure of bovine insulin was first determined by Frederick Sanger in 1951. After that, this polypeptide was synthesized independently by several groups.

Insulin is produced and stored in the body as a hexamer (a unit of six insulin molecules), while the active form is the monomer. The hexamer is an inactive form with long-term stability, which serves as a way to keep the highly reactive insulin protected, yet readily available. The hexamer-monomer conversion is one of the central aspects of insulin formulations for injection. The hexamer is far more stable than the monomer, which is desirable for practical reasons; however, the monomer is a much faster reacting drug because diffusion rate is inversely related to particle size. A fast-reacting drug means insulin injections do not have to precede mealtimes by hours, which in turn gives diabetics more flexibility in their daily schedules.[12] Insulin can aggregate and form fibrillar interdigitated beta-sheets. This can cause injection amyloidosis, and prevents the storage of insulin for long periods.

**Synthesis**

Insulin is produced in the pancreas and released when any of the several stimuli are detected. The stimuli include ingested protein and glucose in the blood produced from digested food. Carbohydrates can be polymers of simple sugars or the simple sugars themselves. If the carbohydrates include glucose, then that glucose will be absorbed into the bloodstream and blood glucose level will begin to rise. In target cells, insulin initiates a signal transduction, which has the effect of
increasing glucose uptake and storage. Finally, insulin is degraded, terminating the response.

**Fig 8: Production and distribution of insulin**

Insulin undergoes extensive posttranslational modification along the production pathway. Production and secretion are largely independent; prepared insulin is stored awaiting secretion. Both C-peptide and mature insulin are biologically active. Cell components and proteins in this image are not to scale.

In mammals, insulin is synthesized in the pancreas within the β-cells of the islets of Langerhans. One million to three million islets of Langerhans (pancreatic islets) form the endocrine part of the pancreas, which is primarily an exocrine gland. The endocrine portion accounts for only 2% of the total mass of the pancreas. Within the islets of Langerhans, beta cells constitute 60–80% of all the cells.
In β-cells, insulin is synthesized from the proinsulin precursor molecule by the action of proteolytic enzymes, known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E. These modifications of proinsulin remove the center portion of the molecule (i.e., C-peptide), from the C- and N-terminal ends of proinsulin. The remaining polypeptides (51 amino acids in total), the B- and A-chains, are bound together by disulfide bonds. Confusingly, the primary sequence of proinsulin goes in the order "B-C-A", since B and A chains were identified on the basis of mass, and the C-peptide was discovered after the others.

The endogenous production of insulin is regulated in several steps along the synthesis pathway:

- At transcription from the insulin gene
- In mRNA stability
- At the mRNA translation
- In the posttranslational modifications

Insulin and its related proteins have been shown to be produced inside the brain, and reduced levels of these proteins are linked to Alzheimer's disease.

**RELEASE**

Beta cells in the islets of Langerhans release insulin in two phases. The first phase release is rapidly triggered in response to increased blood glucose levels. The second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar. The description of first phase release is as follows:
- Glucose enters the β-cells through the glucose transporter GLUT2
- Glucose goes into glycolysis and the respiratory cycle, where multiple high-energy ATP molecules are produced by oxidation
- Dependent on the ATP:ADP ratio, and hence blood glucose levels, the ATP-dependent potassium channels (K⁺) close and the cell membrane depolarizes
- On depolarization, voltage controlled calcium channels (Ca²⁺) open and calcium flows into the cells
- An increased calcium level causes activation of phospholipase C, which cleaves the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate into inositol 1,4,5-triphosphate and diacylglycerol.
- Inositol 1,4,5-triphosphate (IP3) binds to receptor proteins in the membrane of endoplasmic reticulum (ER). This allows the release of Ca²⁺ from the ER via IP3 gated channels, and further raises the cell concentration of calcium.
- Significantly increased amounts of calcium in the cells causes release of previously synthesized insulin, which has been stored in secretory vesicles

This is the main mechanism for release of insulin. In addition, some release takes place generally with food intake, not just glucose or carbohydrate intake, and the β-cells are also somewhat influenced by the autonomic nervous system. The signaling mechanisms controlling these linkages are not fully understood.

Other substances known to stimulate insulin release include amino acids from ingested proteins, acetylcholine released from vagus nerve endings (parasympathetic nervous system), gastrointestinal hormones released by entero endocrine cells of intestinal mucosa and glucose-dependent insulinotropic peptide (GIP). Three amino acids (alanine, glycine and arginine) act similarly to glucose by altering the β-
cell's membrane potential. Acetylcholine triggers insulin release through phospholipase C, while the last acts through the mechanism of adenylate cyclase.

The sympathetic nervous system (via \( \alpha_2 \)-adrenergic stimulation as demonstrated by the agonists clonidine or methyldopa) inhibit the release of insulin. However, it is worth noting that circulating adrenaline will activate \( \beta_2 \)-receptors on the \( \beta \)-cells in the pancreatic islets to promote insulin release. This is important since muscle cannot benefit from the raised blood sugar resulting from adrenergic stimulation (increased gluconeogenesis and glycogenolysis from the low blood insulin: glucagon state) unless insulin is present to allow for GLUT-4 translocation in the tissue. Therefore, beginning with direct innervation, norepinephrine inhibits insulin release via \( \alpha_2 \)-receptors, then subsequently, circulating adrenaline from the adrenal medulla will stimulate \( \beta_2 \)-receptors, thereby promoting insulin release.

When the glucose level comes down to the usual physiologic value, insulin release from the \( \beta \)-cells slows or stops. If blood glucose levels drop lower than this, especially to dangerously low levels, release of hyperglycemic hormones (most prominently glucagon from islet of Langerhans alpha cells) forces release of glucose into the blood from cellular stores, primarily liver cell stores of glycogen. By increasing blood glucose, the hyperglycemic hormones prevent or correct life-threatening hypoglycemia. Release of insulin is strongly inhibited by the stress hormone norepinephrine (noradrenaline), which leads to increased blood glucose levels during stress.

Evidence of impaired first-phase insulin release can be seen in the glucose tolerance test, demonstrated by a substantially elevated blood glucose level at 30 minutes, a
marked drop by 60 minutes, and a steady climb back to baseline levels over the following hourly time points.

**Fig 9: Physiological effect of insulin on glucose uptake and metabolism.**

Insulin binds to its receptor which starts many protein activation cascades. These include translocation of Glut-4 transporter to the plasma membrane and influx of glucose, glycogen synthesis, glycolysis and fatty acid synthesis.

The actions of insulin on the global human metabolism level include:

- Control of cellular intake of certain substances, most prominently glucose in muscle and adipose tissue (about two-thirds of body cells)
- Increase of DNA replication and protein synthesis via control of amino acid uptake
- Modification of the activity of numerous enzymes
- The actions of insulin (indirect and direct) on cells include:
- Increased glycogen synthesis – insulin forces storage of glucose in liver (and muscle) cells in the form of glycogen; lowered levels of insulin cause liver
cells to convert glycogen to glucose and excrete it into the blood. This is the clinical action of insulin, which is directly useful in reducing high blood glucose levels as in diabetes.

- Increased fatty acid synthesis – insulin forces fat cells to take in blood lipids, which are converted to triglycerides; lack of insulin causes the reverse.
- Increased esterification of fatty acids – forces adipose tissue to make fats (i.e., triglycerides) from fatty acid esters; lack of insulin causes the reverse.
- Decreased proteolysis – decreasing the breakdown of protein
- Decreased lipolysis – forces reduction in conversion of fat cell lipid stores into blood fatty acids; lack of insulin causes the reverse.
- Decreased gluconeogenesis – decreases production of glucose from nonsugar substrates, primarily in the liver (the vast majority of endogenous insulin arriving at the liver never leaves the liver); lack of insulin causes glucose production from assorted substrates in the liver and elsewhere.
- Decreased autophagy - decreased level of degradation of damaged organelles. Postprandial levels inhibit autophagy completely.[24]
- Increased amino acid uptake – forces cells to absorb circulating amino acids; lack of insulin inhibits absorption.
- Increased potassium uptake – forces cells to absorb serum potassium; lack of insulin inhibits absorption. Insulin's increase in cellular potassium uptake lowers potassium levels in blood.
- Arterial muscle tone – forces arterial wall muscle to relax, increasing blood flow, especially in microarteries; lack of insulin reduces flow by allowing these muscles to contract.
• Increase in the secretion of hydrochloric acid by parietal cells in the stomach

DEGRADATION

Once an insulin molecule has docked onto the receptor and effected its action, it may be released back into the extracellular environment, or it may be degraded by the cell. The two primary sites for insulin clearance are the liver and kidney. The liver clears most insulin during first-pass transit, while the kidney clears most of the insulin in systemic circulation. Degradation normally involves endocytosis of the insulin-receptor complex, followed by the action of insulin degrading enzyme. An insulin molecule produced endogenously by the pancreatic beta cells is estimated to be degraded within about one hour after its initial release into circulation (insulin half-life ~ 4–6 minutes)

Treatment of Disease

There are several conditions, in which insulin used to treat,

• Diabetes mellitus – general term referring to all states characterized by hyperglycemia

• Type 1 – autoimmune-mediated destruction of insulin producing β-cells in the pancreas, resulting in absolute insulin deficiency

• Type 2 – multifactoral syndrome with combined influence of genetic susceptibility and influence of environmental factors, the best known being obesity, age, and physical inactivity, resulting in insulin resistance in cells requiring insulin for glucose absorption. This form of diabetes is strongly inherited.

Other types of impaired glucose tolerance
- **Insulinoma** - a tumor of pancreatic β-cells producing excess insulin or reactive hypoglycemia.

- **Metabolic syndrome** – a poorly understood condition first called Syndrome X by Gerald Reaven, Reaven's Syndrome after Reaven, CHAOS in Australia (from the signs that seem to travel together). It is currently not clear whether these signs have a single, treatable cause, or are the result of body changes leading to type 2 diabetes. It is characterized by elevated blood pressure, dyslipidemia (disturbances in blood cholesterol forms and other blood lipids), and increased waist circumference (at least in populations in much of the developed world). The basic underlying cause may be the insulin resistance of type 2 diabetes, which is a diminished capacity for insulin response in some tissues (e.g., muscle, fat) to respond to insulin. Commonly, morbidities, such as essential hypertension, obesity, type 2 diabetes, and cardiovascular disease (CVD), develop.

- **Polycystic ovary syndrome** – a complex syndrome in women in the reproductive years where an ovulation and androgen excess are commonly displayed as hirsutism. In many cases of PCOS, insulin resistance is present.