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Review Article

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Review: Sitagliptine-DPP-4 Inhibitor

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Abstract
In these therapeutic time peoples are suffering from various disease. Fight against disease doing some as a research work, discovery of new drugs. In these time biabetes is serious disease. It is two type insuln dependent and non insulin dependent. Sitagliptin is the DPP4 inhibitor which act as Glucagon increases blood glucose levels, and DPP-4 inhibitors reduce glucagon and blood glucose levels. So these drugs are useful for treatmenat of diabtes.
Key words: Disease, research, diabetes, saxigliptine

Introduction
The active substance is sitagliptin as monohydrate phosphate salt and its chemical name is 7-[(3*R*)-3 amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4- triazolo[4,3-*a*]pyrazine phosphate (1:1)

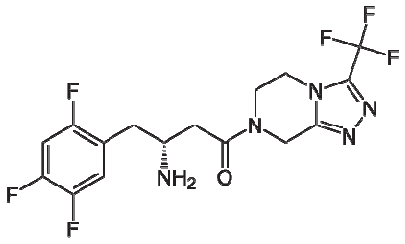


Figure.1

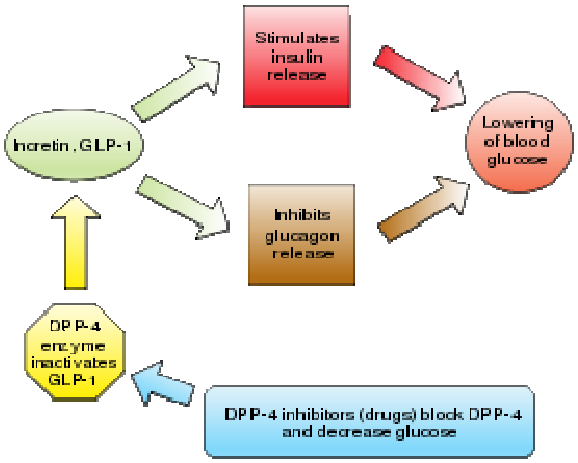
Type 2 diabetes is the most common form of the disease, accounting for about 90% to 95 % of all diagnosed cases of diabetes. In type 2 diabetes, the body does not produce enough insulin or the cells ignore the insulin(Dinesh k. badyal et al2008). Over time, high blood sugar levels can increase the risk for serious complications, including heart disease, blindness, nerve damage and kidney damage. Any new oral hypoglycemic drug that can increase the control of blood glucose with fewer adverse effects in patients with diabetes may be welcomed. Sitagliptin is the first (Dinesh k. badyal 2008) And only prescription medication in a new class of oral antihyperglycemic agents, which enhance the bodies own ability to lower blood glucose when it is elevated.

Like vildagliptin, sitagliptine is an inhibitor of the enzyme dipeptidylpeptidase - 4, an enzyme responsible, among other roles, for the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1 insulinotropin), which plays a role in regulating insulin secretion. It is used in the treatment of type 2 diabetes mellitus, as monotherapy or as dual therapy with metformin, a sulfonylurea, or a thiazolidinedione. Triple therapy using sitagliptin with metformin and a sulfonylurea may be given if dual therapy is inadequate. Sitagliptin is given as the phosphate, but doses are in terms of the base 128.5 mg of sitagliptine phosphate is equivalent to about 100 mg of sitagliptine. The usual oral dose is the equivalent of 100 mg of sitagliptine once daily, as monotherapy or in combination. When given with metformin in a combination preparation, sitagliptine may be given in 2 divided doses. The dose of sulfonylurea may need to be lowered when used with sitagliptine. Sitagliptine may be taken with or without food. Dosage should be

adjusted in patients with renal impairment. Adverse effects reported with sitagliptin include upper respiratory-tract infections, headache, and nasopharyngitis. Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, rash, and Stevens-Johnson syndrome have also been reported.

MOA

Sitagliptin prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretin hormones glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) resulting in enhanced. Glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1 enhances insulin secretion in the presence of raised blood glucose levels, inhibiting DPP-IV activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma. Sitagliptin reduces hemoglobin A1C (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion and Inhibition of glucagon secretion. GLP-1 has other widespread effects including delaying gastric emptying, significantly reducing glucagon's levels and possible central effects on the appetite. Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretins GLP-1 and GIP, gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes, thus tending to prevent an "overshoot" and subsequent low blood sugar (hypoglycemia) which is seen with some other oral hypoglycemic agents. It is slightly less effective than metformin when used as a monotherapy and does not cause a weight gain compared to sulfonylureas. Sitagliptin is recommended as a second line drug (in combination with other drugs) after the treatment based on a combination of diet and metformin fails.



DPP-4 inhibitors and GLP-1

Inhibitors of dipeptidyl peptidase 4, also DPP-4 inhibitors or gliptins, are a class of oral hypoglycemics that block DPP-4. They can be used to treat diabetes mellitus type 2.The first agent of the class - sitagliptin - was approved by the FDA in 2006.

Glucagon increases blood glucose levels, and DPP-4 inhibitors reduce glucagon and blood glucose levels. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.Inhibitors of dipeptidyl peptidase 4, also DPP-4 inhibitors or gliptins, are a class of oral hypoglycemic that block DPP-4. They can be used to treat diabetes mellitus type 2. Glucagon increases blood glucose levels, and DPP-4 inhibitors reduce glucagon and blood glucose levels. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels. Inhibitors of dipeptidyl peptidase 4, also DPP-4 inhibitors or gliptins, are a class of oral hypoglycemics that block DPP-4. They can be used to treat diabetes mellitus type 2. *Metabolism: In vitro* assays indicated that at clinically relevant concentrations, sitagliptin did not inhibit cytochrome P450s or Pgp, nor did it induce human CYP3A4. The sitagliptin metabolites, which were present at low to trace levels in plasma, were

formed by N-sulfation, N-carbamoyl glucuronidation, hydroxylation of the triazolopiperazine ring, and by oxidative desaturation of the piperazine ring followed by cyclization via the primary amine. All the metabolites detected in human plasma were observed in rat and dog, however, not all observed metabolites were present in the same matrix as observed in humans. Due to the minor metabolism of this compound, consequences of the differences in metabolism between human, rat and dog on the observed pharmacokinetics are not expected. The observed *in vitro* metabolism was in agreement with the *in vivo* metabolism. Only metabolite M1 was not observed *in vitro*.

Excretion: *In vitro* plasma protein binding was low in mouse, rat, rabbit, dog, and human. Sitagliptin was excreted primarily unchanged in human, rat and dog. In dogs and humans, sitagliptin was cleared primarily by renal excretion of parent drug, while in rats it was cleared by both renal and biliary excretion. Approximately 5 to 16% of a radiolabeled dose was recovered as phase I and II metabolites in the excreta. Furthermore, sitagliptin observed in bile from dogs was significantly lower than in human faeces and rat bile. Sitagliptin was secreted into rat milk; this is mentioned in section 5.3 of the SPC. As it is unknown if sitagliptin is excreted into human breast milk, it should not be used.

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