

Voglibose: An Alpha Glucosidase Inhibitor

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ABSTRACT

Diabetes Mellitus (DM) is a morbid disease worldwide, with increasing incidence as time passes. It has macro-vascular and micro-vascular complications. The main cause of these complications is poorly controlled postprandial hyperglycaemia. Alpha glucosidase inhibitors, namely acarbose, voglibose and miglitol, are available for therapy. Voglibose is well tolerated and effective in comparable doses among these drugs. This article highlights the important features of voglibose.

Keywords: Postprandial hyperglycaemia (PPHG), Alpha glucosidase inhibitors (α GI)

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder affecting people worldwide, with significant morbidity and mortality caused by its micro-vascular and macro-vascular complications, affecting various vital organs and structures in humans.

It has been estimated that by year 2030, the diabetic population will rapidly increase from 21.7 million to 79.4 million in India. However, prevalence is much more than this estimation, as many patients are asymptomatic and unaware about this and go undiagnosed. This accounts for nearly another one-third of estimated cases [1].

Although now various agents are available for control of mainly type 2 DM normalization of blood glucose, seldom has this been achieved. Recent studies and trials have proved that early detection of DM symptoms and prompt treatment with normalization of blood glucose will decrease the number and severity of diabetic complications.

Another set of patients include patients with Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG), in which glucose levels are above normal, but not high enough to label them as diabetics. Such patients are also prone to development of frank DM or diabetic complications later in life. Loss of early insulin secretion response, along with insulin resistance, results in development of Post-Prandial Hyperglycaemia (PPHG).

In diabetic patients also, PPHG is a direct and independent risk factor for development of Cardiovascular Diseases (CVD) or stroke [2] caused by premature atherosclerosis [2]. Fasting Plasma Glucose (FPG), if high, also leads to some complications in long run if it is not controlled.

PPHG is the major determinant of HbA1c levels. Reduction in PPHG significantly [3] reduces HbA levels in Type 2 DM patients. So, when treating frank DM or IGT or IGF, PPHG level is a major factor which requires aggressive control.

The latest American Diabetes Association guidelines show that [4] lowering glycated haemoglobin (HbA1c) to below or around 7% has been shown to reduce microvascular and neuropathic complications of diabetes and, that if it is implemented soon after the diagnosis of diabetes, it is associated with a long-term reduction of macrovascular disease. Therefore, a reasonable HbA1c goal for many non-pregnant adults is < 7%.

Moreover, The United Kingdom Prospective Diabetes (UKPD) study showed that for every 1% reduction in HbA1c levels, there was an average reduction in micro-vascular complications of 21%, with a maximum reduction of 35%. The risk of myocardial interaction

and sudden death were reduced by 16%. There has been an 18% reduction in fatal and non fatal myocardial infarctions for every 1% reduction in HbA1c levels.

A study done to prevent non-insulin dependent diabetes mellitus (to stop NIDDM) showed that in subjects with IGT, who were treated with α -glucosidase inhibitor (α -GI), it specifically reduced PPHG and 30y. It not only caused reduction in the risk of progression to frank DM, but also caused a 34% risk reduction in development of new cases of hypertension and a 49% risk reduction in CVD [5].

Voglibose is a more potent and tolerant α glucosidase inhibitor (α -GI) as compared to Acarbose and Miglitol.

VOGLIBOSE

Class: Voglibose belongs to class of competitive α glucosidase inhibitors (α -GIs).

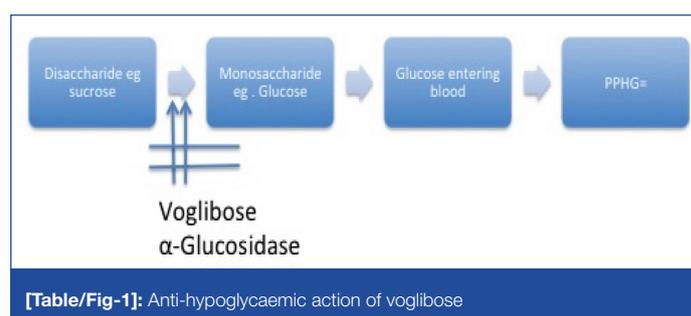
It was discovered in Japan in 1981, after its isolation from *Validamycin* on culture media-the producing organism being *Streptomyces hygroscopicus* var. *limonensis*. But, it became commercially available treatment of DM in Japan since 1994.

CLINICAL PHARMACOLOGY

Mechanism of Action

The anti-hypoglycaemic action of voglibose results from a reversible inhibition of membrane bound intestinal α glucosidase hydrolyze enzymes which hydrolyze oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine.

Thus, voglibose delays the absorption as well as digestion of dietary polysaccharides by reversibly inhibiting carbohydrate digestive enzymes like sucrose, maltose, zomaltase, etc. This results in a reduction in PPHG [Table/Fig-1].



[Table/Fig-1]: Anti-hypoglycaemic action of voglibose

Voglibose may also facilitate mobilisotary α endogenous glycogen-like peptide 1 (GLP-1), which has an inhibitory action on glycogen, thus lowering fasting glucose levels too. Voglibose treatment has resulted in an increased release of GLP-1, which is an insulinotropic hormone and it has also increased release of GLP-1, which is known to enhance insulin secretion and insulin sensitivity [5].

Voglibose has no inhibitory activity against lactase and so, it does not cause lactose intolerance and diarrhoea.

It also has also shown an addictive effect with other Oral Hypoglycaemic Agents (OHAs) like sulfonylurea. It also diminishes the insulinotropic and weight increasing effects of sulfonylureas.

Indications

Voglibose is used in DM for reduction in PPHG, only when diet and/or exercise with lifestyle modification or OHAs or insulin preparations, in addition to diet and/or exercise, do not result in an adequate glycaemic control.

Thus, voglibose is indicated in:

- In NIDDM patients as immunotherapy:** Voglibose is indicated as an adjustment to diet and exercise to improve glycaemic control in patients with NIDDM, where normoglycaemia cannot be achieved by diet alone.
- In combination with other OHAs:** Voglibose is used in potent NIDDM in combination with sulfonylurea or metformin when proper an adequate glycaemic control ie. post-prandial glucose level is not achieved with monotherapy with OHAs [4, 6, 7].
- In addition to insulin in DM patients:** addition of oral voglibose to insulin improves post-prandial blood glucose elevators and it reduces glycosylated haemoglobin in IDDM patients with an impaired glycaemic control [8].
- In elderly patients and in those with hepatic dysfunction or mild to moderate renal impairments in whom other OHAs are contraindicated or they need to be used with caution, voglibose will be helpful.
- Prevention of Type 2 DM:** Kawamori et al., [9] conducted a study to assess whether voglibose could prevent Type 2 diabetes developing in high-risk Japanese subjects with IGT. Voglibose was administered in 897 patients, while 883 received placebo; the study was planned for treatment to be continued until participants developed Type 2 diabetes or for a minimum of 3 years. An interim analysis significantly favoured voglibose; subjects who were treated with voglibose had a significantly lower risk for progression to Type 2 diabetes than placebo (50/897 vs. 106/881: hazard ratio 0.595). Also, significantly more subjects in the voglibose group achieved normoglycaemia as compared to those in the placebo group (599/897 vs. 454/881: hazard ratio 1.539).

Other implications:

- In glycogen storage disease:** Voglibose is helpful in prevention of hypoglycaemia in patients with type Ib glycogen storage disease, it being an amylase (α glycosidase) inhibitor.
- In non-diabetic hyperinsulinaemia, voglibose is helpful in preventing hypoglycaemic attacks.
- In steroid induced diabetes mellitus also, voglibose is helpful. However, clinical data in this setting are limited.
- A potent antimelanogenic agent:** A recent report demonstrated that Voglibose was a representative anti-diabetic drug possessing inhibitory activity towards human α -glucosidase; it blocked the proper N-glycan modification of tyrosinase, resulting in a dramatic reduction of the tyrosinase protein level, by altering its stability and subsequently decreasing melanin production [10].

Usage and Administration Information

Dosage of voglibose must be individualized on the basis of tolerance and effectiveness observed in patients. Total dose of maximum recommended dose of 0.6 mg, three times a day, should not be exceeded.

In NIDDM patients, a dose of 0.2 mg tid before meals has been effective and it has been recommended. Voglibose should be co administered in conjunction with diet treatment or diet plus oral hypoglycaemic drugs and dose titration must be recommended only if a response is not seen with 0.2 mg tid of voglibose.

The higher dose (0.3 mg three times daily) is effective in decreasing the reaction of VAT (visceral adipose tissue) to SATC (Subcutaneous Adipose Tissue) and glycaemic control was related to changes in VAT but not SATC.

Some investigations recommend the use of voglibose only in patients who have an active satisfactory fasting glucose level (<140mg/dl) with strict diet plus sulfonylurea therapy, but who still have significant post-prandial glucose elevations (> 200mg/dl).

For IDDM patients, dose of 0.2 to 0.3 mg tid before meals is administered along with insulin administration [8].

In non-diabetic hyperinsulinaemia and steroid included diabetes, voglibose can be given in dose of 0.2mg tid before meals. In glycogen storage disease, 0.1mg voglibose with lunch and dinner reduces incidence of hypoglycaemic episodes as compared to that in cases who are given no treatment [11].

Koh et al., reported that Voglibose Oral Disintegrated Tablet (VODT) had a similar efficacy as the conventional tablet, but that it improved medication compliance, which in turn could lead to an improved glycaemic control. This VODT was first introduced in Japan in 2004 and it has been available freely in Asian markets since then [12].

Pharmacokinetics [13]

Absorption: voglibose is poorly absorbed after oral administration. However, systematic adverse effects have been observed.

Metabolism: the metabolism of voglibose in liver is negligible.

Excretion: The renal excretion is negligible and plasma concentrations after oral dose have been undetectable.

Overdoses

Unlike sulfonylureas or insulin, an overdose of voglibose tablets will not result in hypoglycaemia.

An overdose may result is transient increase in flatulence, diarrhoea and abdominal discomfort. Because of lack of extra-intestinal effects soon with voglibose, no serious systemic reactions are expected in the event of an overdose.

Contraindications: Voglibose is contraindicated in:

- Hypersensitivity to the drug or to any of its components.
- Diabetic ketoacidosis.
- Inflammatory bowel disease, colonic ulcerations or partial intestinal obstructions and patients being predisposed to intestinal obstruction.
- Chronic disorders associated with marked disorders of digestion or absorption, with conditions that may deteriorate as a result of increased gas formation in the intestine.

Drug Interactions

Voglibose should be administered with caution when it is co administered with the following drugs:

Anti-diabetic drugs and insulin

Derivatives of sulfonamide and sulfonylurea, bigluconide derivatives, insulin preparations and agents used for improving insulin resistance.

Hyperglycaemia occurs when voglibose is used in combination with such agents, so to avoid a possible risk of hypoglycaemia, lower doses should be started with and they should be monitored till optimum dose is revealed.

Voglibose should be used in caution in its concomitant use with anti-diabetic drugs and drugs which enhance the hypoglycaemic action of anti-diabetic drugs such as Beta blockers, salicylates, MAO inhibitors and fibrates.

Similarly, voglibose should be used with caution in its concomitant use with anti-diabetic drugs and drugs which diminish the hypoglycaemic action of anti-diabetic drugs such as epinephrine, adrenocortical hormone and thyroid hormones.

SPECIAL PRECAUTIONS

1. **Pregnancy:** Voglibose falls in the category of B drugs used for pregnant women. The safety of voglibose in pregnancy has not been established. However, no adequate and well controlled studies have been done on pregnant women.

In pregnancy, some degree of systemic absorption occurs. But to prove or disprove it, no animal or human data are available.

2. **Lactating and Nursing Mothers:** Although the levels of voglibose reached in human milk are exceedingly low, it is recommended that voglibose may not be administered to such women.

3. **Paediatric Use:** Only limited data is available. However, it can be used for treatment of glycogen storage disease, to prevent hypoglycaemic episodes.

4. **Liver Diseases:** However negligible is the metabolism of voglibose in liver, it should be used with caution in liver diseases. Hepatotoxicity may occur in some patients. Rise in liver enzymes has been observed in upto 20% of patients during therapy. Cases of hepatitis with severe cholestasis attributed to voglibose hypersensitivity, have been reported.

5. **Renal Function Impairment:** However negligible renal excretion is, voglibose should be used with caution in patients with renal function impairment. Pharmacokinetic studies done on patients with renal insufficiency are lacking.

6. **Gastro-Intestinal Disorders:** Mainly in diarrhoeal diseases, voglibose is to be used with caution. Due to less transit time, it may not be effective.

Bloody diarrhoeal disorders in which ulceration in GI tract occurs, systemic absorption of voglibose may occur. So, it is to be used with caution or it should not be used. In patients with a history of laparotomy or ileus, intestinal obstruction like symptoms are liable to develop, due to an increase in intestinal gas. In patients with chronic intestinal disease, its use may be accompanied by a disturbance in digestion and absorption.

7. **Endocrine and/or Metabolic Disorders:** Episodes of hypoglycaemia have occurred in some patients during voglibose therapy.

ADVERSE REACTIONS

1. **Gastro Intestinal Tract:** Most common side effects are seen in up to 25% of patients and they include soft stools or diarrhoea, flatulence, bloating, abdominal pain or discomfort, abdominal fullness and nausea.

These side effects are mainly caused by unabsorbed carbohydrates in the gut. With continuation of therapy and reassurance of patients, these side effects gradually decrease. Voglibose, however, does not alter rate of gastric emptying.

These side effects, though they are seen more with other α G1 agents such as acarbose, show a slightly lower incidence with voglibose.

Voglibose, along with other α G1 agents, have shown to induce pneumatosis intestinalis in a few cases. This is a rare condition, but it should always be ruled out in diabetic patients who are on alpha GI therapy, who complain of gastrointestinal symptoms. The gastrointestinal tract should be thoroughly investigated in these patients [14].

2. **Liver:** Upto 20% of patients, during therapy with voglibose, show a rise in liver enzymes. One case of hepatitis with severe cholestasis, linked to voglibose hypersensitivity, has been reported.

3. Metabolic hypoglycaemic episodes are not uncommon in patients who are on voglibose therapy.

4. **Central Nervous System:** Nausea vomiting, dizziness have been reported, 10-20 minutes after oral voglibose therapy may be required in such patients.

It occurs mostly in elderly patients in whom micro/ macro angiopathies have already set in. Increase in micro or macro circulatory disturbances resulting from transient reversible reduction in circulatory fluid volume, may be responsible for this side effect, which in turn is mediated by an intra-vascular to gastrointestinal fluid shift caused by presence of undigested oligosaccharides.

Utility of Voglibose in Type2 DM in Combination [6]

Combined use of α G1 and sulfonylurea drugs may be effective in controlling plasma glucose in patients with Type 2 DM and this might delay the onset of vascular complications in these patients [15].

On the other hand, this combination therapy prolongs the derivation of a good glycaemic control as compared with sulfonylurea alone, in Type 2 DM patients [16].

A double blinded placebo-controlled trial showed that in patients with uncontrolled type diabetes mellitus, who experienced inadequate glycaemic control while on voglibose plus diet/exercise therapy, addition of once daily alogliptin to voglibose monotherapy produced clinically significant improvements in glycaemic control, and this was well tolerated [17].

A recent double blinded trial proved that a fixed-dosed mitglinide/voglibose combination significantly improved the glycaemic parameters of HbA1c, GA and 1,5-AG by reducing postprandial glycaemic excursions in patients with Type 2 diabetes mellitus who had switched therapy from glinides or α -GIs [18].

In newly diagnosed Type 2 DM patients who have excess Visceral Adipose Tissue Area (VAT) and Subcutaneous Adipose Tissue (SAT), diet with voglibose therapy effectively reduced VAT which was closely related to an impaired glycaemic control [19].

Voglibose has also been shown to improve obesity in patients with Type-2 diabetes mellitus which was associated with metabolic syndrome [20].

Negishi et al., reported that voglibose treatment prevented the increase of body weight which was induced by pioglitazone in Type 2 diabetes patients and that it may be a potentially useful drug for increasing the benefit of pioglitazone treatment, as it controlled body weight [21]. Also, this combination can be used as one of the first-line drug treatments for glycaemic control in uraemic Type 2 diabetes, as was reported by Abe et al., [22].

Utility of voglibose in non diabetic patients: voglibose improves insulin sensitivity and dyslipidaemic states in non diabetic hyperinsulinaemic subjects too. Treatment with voglibose results in a significant decline of triglycerides and in elevation of HDL cholesterol and apolipoprotein A-I [23].

Voglibose may be helpful as an antiatherosclerotic drug and it reduces the progression of carotid intima media thickness [24,25].

Voglibose in comparison to acarbose and miglitol

50mg acarbose and 0.3mg voglibose produced similar overall effects on post-prandial hyperglycaemia as well as subjective symptoms.

However, marked interindividual variations existed. Subjective symptoms may be a predictor of the divergent clinical response to each agent [26].

On the other hand, voglibose (0.2mg) and acarbose (100mg), thrice daily, significantly reduced HbA1c, PPBG and postprandial insulin levels. At these dose levels, voglibose was associated with lesser gastrointestinal side effects [27].

Key Features of Voglibose in Comparison to Those of Acarbose and Miglitol

At present, 3 glucosidase inhibitors are available for the treatment of patients with DM, which include voglibose, acarbose and miglitol.

Common observation among alpha glucosidase inhibitors, is that glucosidase enzyme inhibition results in delayed carbohydrate digestion and absorption, with attenuation of post-prandial hyperglycaemic excursions. The outstanding feature is that although carbohydrate absorption is delayed, the total amount of carbohydrate absorbed is not altered and that therefore, there are no nutritional caloric losses.

Voglibose, like acarbose, has been associated with an increase in glucagon like peptide (GLP-1), which has insulinotropic effect and which has inhibitory effects on glucagon secretion, which results in overall reduction post-prandial hyperglycaemia.

The inhibitory activity of voglibose on maltose and sucrose is 190-270 times higher than that of acarbose and it is 100 times higher than that of miglitol. However, voglibose has a much weaker inhibitory effect on pancreatic alpha amylase enzyme as compared to acarbose and voglibose is a selective disaccharidases inhibitor [28].

The overall clinical efficiencies of voglibose, acarbose and miglitol in reduction of average post-prandial glucose levels by approximately 50 mg/dl and fasting plasma glucose levels of 10-20mg /dl with reduction in HbA1c by approximately 1%. As a general rule, higher the baseline HbA1c level, greater is the decrease in HbA1c after therapy with α GI.

Also, both voglibose and acarbose proved to significantly increase reversion of IGT to normal glucose tolerance [9,29] and to provide a 49% relative risk reduction in the development of cardiovascular events in patients with IGT.

With reference to adverse drug events, voglibose is more tolerant and it has less drug reactions as compared to Acarbose or Miglitol, due to its relatively lower doses.

SUMMARY

Thus, voglibose potentially provides another therapeutic option for patients with Type 2 diabetes mellitus in which glycaemic control is inadequate, despite diet alone or with pharmacological therapy with sulfonylurea and biguanide. Voglibose may further delay the necessity of initiation of therapy in Type 2 diabetes patients.

Voglibose may reduce insulin dose requirement in Type 1 diabetes patients.

Voglibose improves post-prandial hyperglycaemia and FBS in NIDDM patients who are poorly controlled, despite strict diet control and taking other oral hypoglycaemic agents.

Thus, voglibose is effective and it is generally well tolerated in a wide range of Type 2 diabetic mellitus patients.

So voglibose:

- Is an α glucosidase inhibitor (α GI) which inhibits glucose hydrolyzing enzyme-glucosidase (maltose) and which decreases carbohydrate absorption and decreases PPHG.

- Mobilizes endogenous pool of insulinotropics.
- Has better tolerability than Acarbose.
- Does not alter rate of gastric emptying.

Voglibose is useful in elderly patients and in those with hepatic impairment or mild to moderate renal function impairments when other anti diabetic agents are contraindicated. It needs to be used with caution.

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Date of Submission: **Apr 30, 2013**
Date of Peer Review: **Aug 09, 2013**
Date of Acceptance: **Sep 30, 2013**
Date of Publishing: **Dec 15, 2013**

FINANCIAL OR OTHER COMPETING INTERESTS: None.