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Alfa Glucosidase Inhibitor: Voglibose Can Prevent Progression Of Impaired Glucose Tolerance Stage To Type II Diabetes Mellitus.

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ABSTRACT

Carbohydrate rich diet is an important constituent of Indian menu and contributes a major role in plasma glucose level.α-glycosidase is an enzyme present in the intestinal brush border which is responsible for digestion of oligosaccharide like maltose, maltotriose and dextrins and produces monosaccharide like glucose, galactose and fructose which are rapidly absorbed across the wall of the small intestine. Alfa glucosidase inhibitors like acarbose, voglibose and miglitol inhibits the action of alfaglucosidase and reduces post prandial hyperglycemia. It also increases the release of the glucoregulatory hormone GLP-I which has favorable effect on blood glucose. Voglibose may also facilitate secretion of gastrointestinal peptides such as glucagon like peptide-1 (GLP-1) and glucagon inhibitory peptide (GIP). When voglibose is taken with a meal rich in carbohydrates, GIP secretion is decreased while GLP-1 is markedly increase, especially in the late post prandial period. Voglibose has been clinically used as a drug which improves glucose tolerance by inhibiting digestion and absorption of glucose from intestine. Another advantage of voglibose is that it decreases post prandial glucose without inducing hypersecretion of insulin. Voglibose also reduces the progression of intimal medial thickness (IMT) and may be a candidate for an anti atherosclerotic drug for tyupe-2 DM patients Voglibose therapy inhibited cardiac remodelling by decreasing myocardial oxidative stress in mice with cardiac pressure overload. In this review we summaries the effects of long term voglibose treatment on changes in fasting blood glucose level together with changes in glycosylated Hb level.

Keywords: voglibose, PPBS, Diabetes, FBS, glycosylated Hb, acarbose, Metformin

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BACKGROUND OF REVIEW

Diabetes mellitus is a major global health problem and an increasing cause of morbidity and mortality. The term diabetes mellitus describes a metabolic disorder of multiple aetiology, characterized by chronic hyperglycemia with disturbance of carbohydrate,fat and protein metabolism [1]. Post prandial hyperglycemia otherwise known as Impaired Glucose Tolerance stage (IGT), is a stage of impaired glucose regulation that is present in individuals whose glucose tolerance is above the conventional normal range but lower than the level considered diagnostic of type-ll diabetes mellitus . IGT represents transient stage between normal glucose tolerance and type-llDM [2]. It has been reported that alfa-glucosidase inhibitors like acarbose, voglibose and miglitol inhibits alfa-glucosidase and reduces post prandial hyperglycemia and thereby improves glucose tolerance.Voglibose has been clinically used as a drug which improves glucose tolerance by inhibiting digestion and absorption of glucose from intestine. Another advantage of voglibose is that it decreases post prandial glucose without inducing hypersecretion of insulin. αglucosidase inhibitors competitively block small intestinal brush enzymes that are necessary to hydrolyzeoligo and polysaccharides to monosaccharide [3]. Normally carbohydrates are primarily and rapidly absorbed in the first half of the small intestine with α glucosidase inhibition. Carbohydrate absorption and digestion occur throughout the small intestine. This results in slower absorption of ingested carbohydrates and consequently the post prandial plasma glucose rise is blunted [4].

INTRODUCTION

Acarbose is a pseudotetrasaccharide of microbial origin produced by a permentation process involving a bacterium Actinoplanesutahensis [5]. It was isolated and purified in the late 1970s and approved for the treatment of type 2 diabetes in the early 1990s [6] . Acarbose structurally analogous to an oligosaccharide derived from starch digestion. It is made up of a maltose unit link to an acarviosine unit, which represents the active part of the molecule. The acarviosine unit has nitrogen linkage, which is responsible for its high affinity for the carbohydrate binding site of various α glucosidases and exceeds the affinity (10-100000 fold) of regular oligosachharides from nutritional carbohydrates. Because of this C-N linkage, acarbose cannot be cleaved and therefore, enzymatic hydrolysis is blocked. Despite its high affinity for these enzymes, acarbose binding is reversible and its inhibition kinetics are competitive owing to its specificity for α glucosidases, β glucosidases (e.g. lactose) are not inhibited by acarbose and so lactose digestion and absorption are not affected by it. Intestinal glucose absorption is also not impacted by α – glucosidaseinhibitors [7,8]. Because acarbose is poorly absorbed (less than 1.2 % of the active compound) it displays its inhibitory activity not only in the proximal jejunum but all along the small intestine up to the ileum .Acarbose is cleaved in the large intestine by bacterial enzymes into several metabolites. Thus even though acarbose itself is poorly absorbed, 35 % of an oral dose appears as metabolites in urine .Miglitol is synthetic derivative competitive and reversible inhibitors with a shorter duration of action than acarbose. It is rapidly absorbed in the jejunum through a transport mechanism identical to glucose, but is quantitatively exerted unchanged by the kidney. Further experimental compounds include castanospermine (MDL 73945), an irreversible inhibitor of alpha glucosidase.

DISCUSSION

Voglibose is valiolamine derivative and is the potent α- glucopsidase inhibitor. Voglibose inhibits most α- glucosidase enzymes but is weaker than acarbose at inhibiting sucrose and has little effect on pancreatic amylase. Neither acarbose nor voglibose interferes with glucose absorption through the intestinal sodium dependent glucose transporter. Aglucosidase inhibitors must be present at the site of enzymatic action at the same time as the oligosaccharide or disaccharide. Therefore they should be taken with the first bite of meal . The delay in carbohydrate digestion and absorption in the small bowel increases the amount of fermentable carbohydrates reaching the colon. This results in gastrointestinal symptoms (flatulence, diarrhea).

In type-2 diabetic patients suboptimally controlled with metformin, the addition of acarbose produced a mean reduction of 0.8 % in HbA1c, 1.2 mmol/l in fasting plasma glucose and 2.95 mmol/l in past prandial plasma glucose [9-11].

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VOGLIBOSE

Chemistry: Voglibose is an N-substituted derivative of valiolamine.

Systematic IUPAC name:

(1S,2S,3R,4S,5S)- 5 – (1,3- dihydroxypropan – 2 – yalomino) – 1 – (hydroxyl methyl) cyclohexane - 1,2,3,4 – tetraol

Formula: $C_{10}H_{21}NO_7$

Molecular weight: 267.28 gm/mol

It was discovered in Japan in 1981. Its isolation from validomyan on culture media. Voglibose is of microbial origin from Streptomyces hygroscopicies var. limonons [12]. It became commercially available for treatment of DM in Japan since 1994.

Voglibose may also facilitate secretion of gastrointestinal peptides such as glucagon like peptide-1 (GLP-1) and glucagon inhibitory peptide (GIP). When voglibose is taken with a meal rich in carbohydrates, GIP secretion is decreased while GLP-1 is markedly increase, especially in the late post prandial period

Figure1: Comparative distribution of FBS of Different Treatment Groups(Box Plot)[2]

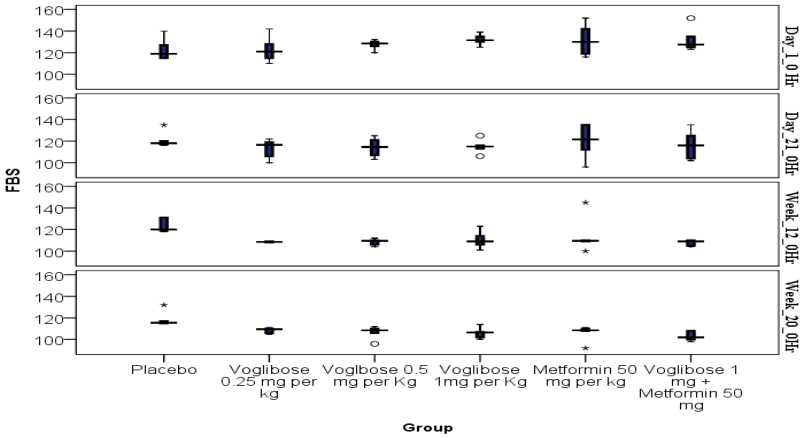
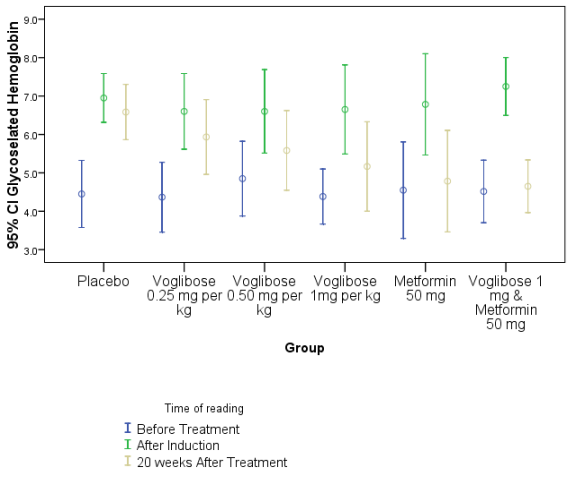


Figure 2: Compairsion of Mean Glycosylated Haemoglobin along with 95% CI by Treatment Group[2]



Review of some of the studies related to voglibose

Voglibose one of the most important alpha glucosidase inhibitor delays the digestion and absorption of carbohydrates, thereby inhibiting post prandial hyperglycemia and hyperinsulinemia [13-16]. This is another reported advantages of voglibose is that they decreases post prandial glucose without inducing hyper secretion of insulin [14,15]. This effect is desirable in treatment of NIDDM patients for at least two reasons:Hyperinsulinemia may be related to the development of coronary artery disease, and hypersecretion of insulin may result in exhaustion of pancreatic β cells [(16) (17)].Figure 1.shows voglibose at different doses and metformin decreases fbs level at different time period in animal model[(2)]. Manas et al ,reported there is significant decrease in Glycosylated Hb value in alloxan induced diabetic rabbits as shown in figure 2 [2].

Kazunari Matsumoto et al reported that the patients treated with voglibose showed a statistically significant decrease in insulin secretion [18]. These results agreed with reports of previous studies including other α- glucosidase inhibitors [14,15,19,20], indicating that voglibose may reduce insulin secretion in NIDDM patients.

Kahn et al reported that both insulin secretion and insulin sensitivity were important factors in determining glucose tolerance [21]. According to KazunariMatsumato et al insulin sensitivity increased with statistical significance in patients treated with voglibose [18]. Improvement in insulin sensitivity was probably attributable to the improvement in glycemic control [22].

Kazunari Matsumato et al reported that the decrease in post prandial plasma glucose may result in a decrease in the intrinsic insulin secretion and may inhibit the overwork of the pancreatic β cells. Again this study concluded that voglibose treatment decreases intrinsic insulin secretion, probably via the delay in intestinal absorption of carbohydrates and hence voglibose is considered to be a drug beneficial in the treatment of NIDDM patients.

Prevention of Type-2 DM

Kawamori et al 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 favouredvoglibose; subjects who were treated with voglibose had a significantly lower risk for progression to type-2 diabetes than placebo (50/897 Vs 106/881). Also significantly more subjects in the voglibose group achieved normoglycemia compared to those in the placebo group [23].

Effect of voglibose on lipid profile

Rosenthal SH et al reported that alfaglucosidase inhibitors like acarbose and voglibose lowers TG but its effect is inconsistent [24,25]. The lipid lowering effects of voglibose is due to glycemic control more than a direct action of the drug [26].

A review on the effect of oral hypoglycaemia agents on serum lipids with type-2 DM found beneficial of voglibose on triglyceride. However a meta analysis was not performed. Kazuya et al reported voglibose not only has a direct hypoglycaemic effect through decrease absorption of carbohydrates but also has hypoinsulinemic and hypolipidemic effect via improved insulin sensitivity [27].

Effect on obesity and body weight

Voglibose has also been shown to improve obesity in patients with type-2 diabetes mellitus which was associated with metabolic syndrome [28].

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 [29]. Also this combination can be used as

one of the first line drug treatment. For glycemic control in uraemic Type-2 diabetes, as was reported by Abe et al [30].

Kobatake T. et al, 1989 conducted an experiment on effect of voglibose (AO-128) and concluded that voglibose caused a substantial reduction of mesenteric fat weight accompanied by a marked decrease in fat cell volume in Zucker fatty rats [31].

Effect of voglibose on cardiovascular system

Yoshimitashu Y et al, 2005 reported that voglibose also reduces the progression of intimal medial thickness (IMT) and may be a candidate for an anti atherosclerotic drug for tyupe-2 DM patients [32].

Takashima S et al, 2006 concluded from their experiment on mice that improvement of glycemic control through voglibose therapy inhibited cardiac remodeling by decreasing myocardial oxidative stress in mice with cardiac pressure overload [33].

Some Other Effect of Voglibose

Maruto T et al reported that voglibose significantly prevented hypotension and neurotension increment after glucose intake in patients with neurologic disorder and elderly patients but the mechanism is still unknown [34].

Ihara K, 1998 reported that voglibose was a representative anti diabetic drug possessing inhibitory activity towards human α glucosidase and it blocked the proper N glycan modification of tyrosinase, resulting in a dramatic reduction of tyrosinase protein level by altering its stability and subsequently decreasing melanin production [35].

Voglibose in Combination

Matsumato K et al reported that combined use of alpha glucosodase inhibitor and sulfonyl urea 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 [(36)].On the other hand this combination therapy prolongs the derivation of a good glycemic control as compared with sulfonylurea alone in Type-2 DM patients [37].

A double blind placebo controlled trial showed that in patients with uncontrolled type diabetes mellitus who experienced inadequate glycemic control while on voglibose plus diet/exercise therapy, addition of once daily alogliptin to voglibosemonotherapy produced clinically significant improvements in glycaemic control and this was well tolerated [38]. A recent double blind trial proved that a fixed dose miglitinide/ voglibose combination significantly improved the glycaemic parameters of HbA1c, by reducing post prandial glycaemic excursion in patients with Type-2 DM who had switched therapy from glinides or alfaglucosidase inhibiters [38].

Again Goke B et al 1995 and Takahisa et al 2013 reported voglibose is used in combination with sulfonylurea or metformin when adequate glycaemic control i.e. post prandial glucose level is not achieved [39,40].

Kawamori R et al 2009 reported addition of oral voglibose to insulin improves piost prandial blood glucose elevators and it reduces glycosylated haemoglobin in 10 DM patients with an impaired glycaemic control [41].

Copmparative Studies between Acarbose and Voglibose

Two studies of α glucosidase inhibitors have compared acarbose and voglibose [42,43]. Kageyama S et al reported voglibose 0.2 mg tid and acarbose (100 mg TID) were compared in type-2 diabetic subjects on diet therapy. The study design was a cross over trial of 8 weeks of active treatment versus placebo with 1 month of wash out between two treatment periods. Voglibose was associated with less gastrointestinal side effects, but was also less effective in reducing post prandial blood glucose excursion [42].

Usage and Administration Information: 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.

For IDDM patient's dose of 0.2 to 0.3 mg tid before meals is administered along with insulin administration.

In glycogen storage disease 0.1 mg voglibose with lunch and dinner reduces incidence of hypoglycaemic episodes as compared to that in cases that are given no treatment [44].

Koh et al reported that voglibose oral disintegrating tablet (VODT) had a similar efficacy as conventional tablet but that is improved glycaemic control. This VODT was first introduced in Japan in 2004 and it has been available freely in Asian markets since then.

Adverse Reaction

Gastrointestinal side effects

Vichayanrat A et al reported less abdominal discomfort, abdominal fullness and flatulence bloating than acarbose. These side effects are mainly caused by unabsorbed carbohydrates in the gut. With continuation of therapy and reassurance of patience there side effects gradually decreases.

Voglibose however does not alter rate of gastric emptying.

Liver

Toshikazu Masumato reported a case and drug induced hepatitis with severe cholestasis caused by voglibose. The patient presented with icterus and praritus after 3 months of voglibose treatment. One month after onset of icterus the patient also developed cholangitis due to methicillin resistant staphylococcus accrues and serum total bilrubin level is increased to above 40 mg/dl.

Ajay S Dabhi et al reported that upto 20 % of patients during therapy with voglibose show a rise in live enzymes.

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

Central Nervous System

Ajay S Dhabi et al reported nausea, vomiting, dizziness 10-20 minutes after oral voglibose. It occurs mostly is elderly patients in whom micro or 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 effect, which in turn is mediated by an intravascular to gastrointestinal fluid shift caused by presence of undigested oligosaccharides.

Precautions

- Pregnancy- Voglibose falls in category B drugs for pregnant woman. The safety of voglibose on pregnancy has not been established. However no adequate and well controlled studies have been done on pregnant woman.
- 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.
- Voglibose should be used in caution in Liver disease, renal function impairment, with chronic intestinal disease [45].

- Voglibose is contraindicated in patients with increased generation of gas (e.g. Roemfield syndrome). Voglibose should be administered with caution to patients with history of laparatomy or ileus [45].

CONCLUSION

Treatment with voglibose decreases insulin secretion indirectly through delaying in intestinal absorption of carbohydrate. Voglibose at different doses significantly decreased FBS and HbA1c. By decreasing insulin secretion it indirectly prevents the development of coronary artery disease which is more likely to develop in patients with impaired glucose tolerance. The effect of long term treatment of voglibose is that it can prevent the progression of impaired glucose tolerance to Type II DM.Hence inhibition of digestion and absorption of oligosaccharide have a definite role in control impaired glucose tolerance and may have a role in progress of type -2 DM.

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