New Horizons in Diabetes Therapy - Alpha Glucosidase Inhibitors

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A normal life despite diabetes is only possible when intervention therapy aims at achieving a physiological level of blood glucose and HbA 1c, maintenance of a desirable body weight and serum lipids to avoid hyperinsulinaemia and late diabetes complications and to retard the development of atherosclerosis[1]. The first revolution in the treatment of diabetes came with the discovery of insulin in 1921, before which nearly 64% diabetic subjects died prematurely in diabetic coma[2]. This was followed by the introduction of oral anti-diabetic suiphonylureas and biguanides about 3 decades ago. The suiphonylureas increase endogenous insulin secretion from the beta cells of the pancreas thus lowering the elevated blood sugar levels through a physiological action of insulin. The basic requirement for suiphonylureas to be effective are functioningbeta cells[3]. Biguanides act through a different pathway to produce their hypoglycaemic effect. Several mechanisms have been implicated of which reduction in gastrointestinal glucose obsorption, increased anaerobic glycolysis, inhibition of gluconeogenesis, stimulation of peripheral glucose uptake and increased binding of insulin to its receptor are the most accepted[3]. A new concept introduced in the treatment of diabetes mellitus was the postponement of intestinal glucose absorption. This was achieved by the introduction of a-glucosidase inhibitors in the form of acarbose[4,5]. Delaying glucose absorption in the gut was attempted first by dietary modification. The nutrient load was spread out into frequent small servings throughout the day. This provided a stable blood glucose and prevented steep rises. This holds good for both insulin dependent and non-insulin dependent diabetics. Complex carbohydrates from starchy foods do not raise blood sugar levels as much as simple ones. Fibre in the food slows down carbohydrate absorption and reduces fasting blood glucose, glycosylated haemoglobin and serum lipid levels. Dietary modification does delay glucose absorption but it does not solve the problem of postprandial hyperglycaemia. This leads to the new pharmacological approach through alteration of the activity of intestinal a-glucosidase by using specific inhibitors[6]. Acarbose, isolated from fermentation of actinoptanes strains, is a pseudo-tetrasaccharide of microbial origin[7]. It is a competitive and reversible inhibitor of intestinal a-glucosidase activity[8]. a-glucosidases are located in the luminal brush border formed by enterocytes of the small gut. Since carbohydrates are taken up in the form of monosaccharides only in the intestine, the disaccharides and polysaccharides are broken down by glucosidases before they can be absorbed[9]. In this process cc-glucosidase inhibitors delay carbohydrate digestion leading to delayed glucose absorption. Glucose, fructose and sorbitol which are directly absorbed and un digestable carbohydrates as cellulose, are not affected by the drug. Thus the efficacy of a-glucosidase inhibitors depends on the carbohydrate composition of the meals. Studies conducted with acarbose on non-insulin-dependent diabetic patients demonstrated an improved metabolic control regardless of whether being administered in addition to oral hypoglycaemic agents or to a diet alone[10,11]. The most significant finding was a reduction in the post-prandial blood glucose concentration. Evidence was also had for a reduction in serum insulin levels[12]. Acarbose does not lead to malabsorption of carbohydrates. A diet rich in poorly digestable complex carbohydrates causing an intestinal load will result in bacterial fermentation which can cause flatulence, distension and diarrhoea. Due to an effective assimilation in the large bowel no faecal loss of calories takes place[9]. Studies have been conducted on IDDM patients by adding acarbose to their insulin regime. Post-prandial blood glucose concentrations are reduced, smoother diurnal blood glucose profiles were achieved and in some cases the daily insulin requirement was reduced[13]. The

lipogenic effect of insulin is well documented. It stimulates the uptake of glucose and fatty acids into the fat cells via adipocyte lipoprotein lipase. Insulin reduces fat degradation by inhibiting the hormone sensitive lipase responsible for the cleavage of neutral fat into fatty acid residues and glycerol. This double mechanism results in an increased adipose tissue mass. Insulin also influences the genesis of triglyceride formation. This type of hyperlipo proteinaemia occurs due to the strong correlation between insulin insensitivity and the rate of hepatic VLDL synthesis in prediabetic subjects[14]. Dyslipoproteinaemia is observed in 50 percent of type II diabetics which is an important contributory factor to macroangiopathy. The dyslipoproteinaemic state can either be induced by excessive fat consumption or by hyper in sulinaemia and insulin resistance evoked by diabetes, hypertension and obesity. Acarbose treatment has no effect on the former. When used in the second group a reduction in the serum lipid levels has been observed. The mechanism of action is by restoration of hepatic VLDL metabolism or reduction of VLDL formation by the liver which is secondary to the actions of acarbose upon intestinal sugar digestion and insulin secretion. This beneficial effect has also been observed in type 11 diabetics taking a diet containing 50 percent carbohydrate by caloric value[16]. Less than 2 percent of the orally applied a carbose is absorbed from the intestine. It is excreted by the kidneys in an unaltered form. Toxicity studies revealed no adverse effects[17]. Acarbose is used where dietary hyper-glycaemia exists secondary to intestinal carbohydrate absorption. Monotherapy with acarbose has no associated risk of hypoglycaemia. The addition of acarbose to sulphonyluria therapy in NIDDM patients has an additive effect and the desired therapeutic result can be achieved often with a reduction in the dose of the sulphonyluria. As acarbose acts immediately after ingestion it should be taken with meals. To avoid gastrointestinal symptoms, therapy should be started with a low dose regimen. The dose should be increased under blood glucose control until optimal effects are achieved. The drug is available in 50 and 100mg tablets and the maximum suggested dose is 3x200 mg day. With the introduction of cc-glucosidase inhibitors (acarbose) for the therapeutics of diabetes mellitus especially NIDDM, new horizons have been opened. This drug acting directly on the carbohydrate absorption not only gives an improved glycaemic control but also has beneficial effects on the fat metabolism, thus providing protection from dyslipoproteinaemia.

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