

New drugs in diabetes

H N Rajaratnam¹, S A Kahandawa²

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Abstract

The field of diabetes has witnessed the development of new therapeutic agents with novel mechanisms of action. This article describes four drugs which have the potential for revolutionizing the management of type 2 diabetes in the future.

Colesevelam is a bile acid sequestrant, which is unique in reducing both LDL cholesterol and hyperglycaemia, when used in combination with metformin, sulphonylurea and insulin. Additionally, it is effective in patients with prediabetes and hypercholesterolaemia. Hypoglycaemia and weight gain are not observed with colesevelam.

Bromocriptine mesylate is a timed release dopamine D2 receptor agonist which restores the dopaminergic tone within the central nervous system (CNS). It reduces plasma glucose, triglyceride and free fatty acid (FFA) levels. Additionally cycloset decreased the cardiovascular composite end point by 40%. The drug has to be taken within 2 hours of awakening.

Dapagliflozin is a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor which increases urinary glucose excretion resulting in net caloric loss. It reduces both weight and blood pressure. But dapagliflozin-treated patients reported an increase in events suggestive of genital infections and lower urinary tract infections (UTIs), which needs further evaluation.

Glucokinase (GK) which is involved in the first step in glycolysis, exhibits two different actions in pancreas and liver leading to increased insulin secretion and glycogen synthesis respectively. Glucokinase activators (GKAs) increase the affinity of GK for glucose by ten fold. Long term clinical trials are needed to evaluate the safety of this novel drug.

Introduction

Type 2 diabetes is characterised by elevated blood glucose levels resulting from a pancreatic β -cells secretory insufficiency combined with insulin resistance (1). The disease has a polygenic basis because numerous genes (the latest count exceeding 20) participate in its pathogenesis. But modern lifestyle characterised by limited physical activity and excessive caloric intake are critical precipitating factors for the current epidemic of type 2 diabetes worldwide (2).

Desirable properties of an ideal antidiabetic drug should include effective and sustainable blood glucose reduction, minimal risk of hypoglycaemia, reduction in cardiovascular risk factors and cardiovascular events, weight reduction, safety in the presence of hepatic, renal and cardiac failure, ability to use in combination with existing drugs and cost effectiveness. It appears that existing antidiabetic drugs in use need considerable improvement in their properties, if they are to be compared with the ideal antidiabetic drug. This deficiency has led

to the development of new therapeutic agents which have the capacity, in some aspects, to match the ideal antidiabetic drug.

This article describes four such new antidiabetic drugs (Colesevelam, Bromocriptine, Dapagliflozin and Glucokinase activators) which have the potential for revolutionising the management of type 2 diabetes.

Colesevelam

Bile acid sequestrants (BASs) were developed as lipid lowering agents for the treatment of hypercholesterolaemia. BASs also improve glycaemic control which provides the basis for the use in patients with type 2 diabetes. Colesevelam hydrochloride is the only BAS which was approved by Food and Drug Administration (FDA) for both lipid and glycaemic control (3).

Mechanism of action

Bile acid sequestrants remove bile acid from the intestine, which prevents hepatic recycling required for

¹Consultant Physician and Endocrinologist, Nawaloka Hospital, Colombo, Sri Lanka, ²Senior Registrar in Endocrinology, National Hospital of Sri Lanka, Colombo.

cholesterol synthesis. But the exact mode of glycaemic control remains unexplained. Possible mechanisms include the reduction of endogenous glucose production by the effects on the farnesoid X receptor (bile acid receptor) within the intestine and liver (4). Furthermore BASs may increase the secretion of incretin hormones such as GLP-1 and glucose dependent insulinotropic polypeptide.

Efficacy

In three double blinded studies, the addition of colesevelam (3.75 g / day) to existing antidiabetes therapy resulted in a significant reduction in HbA1c. Placebo-corrected reductions in HbA1c ranged from 0.5% (at 16 weeks on background insulin therapy) to 0.54% (at 26 weeks on background metformin or sulphonylurea therapy). In addition, colesevelam reduced plasma fasting glucose (FBG reduction > 30 mg / dL) relative to the placebo in all three studies (5-7).

Apart from glycaemic benefit, colesevelam resulted in a significant LDL cholesterol reduction (ranging from 12.8% to 16.7%) in patients with type 2 diabetes (5-7). This effect was present even when colesevelam was added to existing statin therapy. HDL cholesterol did not significantly change from baseline. However, triglyceride level increased significantly (18%), when colesevelam was added to sulphonylurea or insulin based therapy. The lipid and apolipoprotein ratios (LDL / HDL cholesterol and apo B / apoA1) indicative of cardiovascular risk were significantly reduced with colesevelam (5-7).

Safety and tolerability

Compliance with colesevelam was 93% in the three double blind studies (5-7), suggesting that it was well tolerated. The most common drug related adverse effects were gastrointestinal in nature (mainly constipation), since these agents bind to bile acids in the intestine. Incidence of hypoglycaemia was similar with colesevelam and placebo. Weight management is an important component of antidiabetic therapy and colesevelam was shown to be weight neutral (3).

Colesevelam is contraindicated in patients with a history of bowel obstruction, serum triglyceride concentration more than 500 mg / dL and with a history of hypertriglyceridaemia induced pancreatitis.

Colesevelam in prediabetes

Individuals with prediabetes are at an increased risk of developing type 2 diabetes and cardiovascular disease. One study showed that colesevelam reduced LDL cholesterol and fasting plasma glucose significantly in patients with hypercholesterolaemia and prediabetes (8). Therefore colesevelam may represent a novel treatment strategy for this population. However, additional research is needed to evaluate whether colesevelam prevents conversion from prediabetes to type 2 diabetes.

Colesevelam in established type 2 diabetes

Many hypoglycaemic agents have reduced efficacy when added as a third or fourth line agent to existing treatment. However, colesevelam has been demonstrated to maintain its efficacy as an add-on therapy (5-7), suggesting this agent provides an added glycaemic benefit regardless of existing diabetes therapy and duration of disease.

Colesevelam is not contraindicated in patients with renal, hepatic or cardiac failure, because it is not systemically absorbed (3). This finding is particularly important in patients with long standing type 2 diabetes who may have either renal or cardiac failure and cannot take medications such as metformin and thiazolidinediones.

Bromocriptine mesylate

In 2009, bromocriptine mesylate, a sympatholytic dopamine D2 receptor agonist was approved by the FDA for the treatment of type 2 diabetes. This centrally acting antidiabetic agent has a novel mechanism of action. It reduces plasma glucose, triglyceride and FFA levels. Additionally, a one year prospective study showed a reduction in cardiovascular events in patients treated with bromocriptine mesylate (9).

Mechanism of action

Bromocriptine is unique in that it does not have a specific receptor that mediates its action on glucose and lipid metabolism. Rather its effects are mediated via resetting of dopaminergic and sympathetic tone within the CNS (10).

As explained by the thrifty gene hypothesis, mammalian species living in the wild have an incredible ability to switch the metabolism from insulin sensitive state to insulin resistant state when food is sparse. This switch provides a survival advantage (11). Insulin resistant state is brought about by decreasing dopamine levels within the ventromedial hypothalamus. Restoration of dopamine leads to an insulin sensitive state (9). This mechanism provides the basis for the use of bromocriptine in type 2 diabetes.

Type 2 diabetic patients are believed to have an early morning dip in dopaminergic tone. Restoration of this deficiency by early morning bromocriptine administration leads to a decline in hepatic gluconeogenesis, reduced adipose tissue lipolysis and improved insulin sensitivity (9). Three clinical trials (12-14) proved that bromocriptine mesylate significantly reduced fasting and postprandial glucose concentrations without a change in serum insulin concentration or body weight. Bromocriptine mesylate has demonstrated a 0.5- 0.7% reduction in HbA1c. It also significantly reduced serum FFA and triglyceride concentrations.

Pharmacokinetics and dose

Bromocriptine mesylate tablets are rapidly dissolved and absorbed within 30 minutes (12). But only 5 - 10% of the ingested dose reaches systemic circulation due to extensive hepatic first pass metabolism (15). Bromocriptine mesylate differs from traditional bromocriptine formulations in its quick release that provides maximum plasma concentration within 60 minutes. The drug is available as 0.8 mg tablets. The starting dose is 0.8 - 1.6 mg / day and the maximum dose is 4.8 mg/day. It is administered as a once daily dose within 2 hours of awakening (9).

Safety and tolerability

The common side effects are nausea (26%), asthenia (15%), constipation, dizziness and rhinitis. There was no significant increase in the incidence of hypoglycaemia, because insulin secretion is not stimulated (12).

Cardiovascular benefits

Bromocriptine mesylate decreased the cardiovascular composite end point by 40% (14), i.e. 79 diabetic patients need to be treated for 1 year to avoid one cardiovascular event. The mechanisms via which bromocriptine mesylate reduce cardiovascular events remains to be identified. The possible mechanisms are its inhibitory effect of CNS sympathetic over-activity on the vasculature and reduction of HbA1c, blood pressure, triglycerides and postprandial FFA levels.

Dapagliflozin

Dapagliflozin is the first in a novel class of glucose-lowering medications, the selective sodium-glucose cotransporter 2 (SGLT2) inhibitors (16). The Food and Drug Administration (FDA) Advisory Committee has not approved dapagliflozin for clinical use due to safety concerns regarding the risk of bladder and breast carcinoma.

Mechanism of action

SGLT2 is expressed in the proximal renal tubule and accounts for about 90% of the reabsorption of glucose from tubular fluid. Dapagliflozin is a selective SGLT2 inhibitor. Therefore these agents increase urinary glucose excretion with resulting net caloric loss (17).

This effect depends on baseline glycaemic control and glomerular filtration rate, but is independent of insulin. Consequently, reduction in plasma glucose with dapagliflozin reduces the glucose load filtered by the kidney and limits further glucose excretion, suggesting that dapagliflozin may possess a low intrinsic propensity for hypoglycaemia (18).

Efficacy

A 52-week duration study revealed that dapagliflozin produced a mean reduction of HbA1c that was statistically non-inferior to the sulfonylurea (glipizide), in patients poorly controlled with metformin monotherapy. This glycaemic control was achieved with 10-fold fewer hypoglycaemic episodes. Weight loss with dapagliflozin was progressive during the first 6 months and stabilized during the latter half of the study (19). This may have resulted from glucosuria induced caloric loss, fluid loss associated with osmotic diuresis, or a combination of both.

Dapagliflozin also reduced blood pressure. The exact mechanism for this effect is unclear, but may involve osmotic diuresis or sodium loss (19).

Adverse effects

Increased urine volume (up to 400 ml) with slight volume depletion was observed in clinical studies with dapagliflozin. But no meaningful changes were noted in electrolytes, serum creatinine or proportions of patients experiencing orthostatic hypotension to indicate dehydration or renal impairment.

Another important question is whether increased glucosuria would predispose to UTIs or genital fungal infections. Dapagliflozin treated patients, especially women, reported an increase in events suggestive of genital infections and lower UTIs (19). But this finding may be due to increased surveillance and anticipation. Hence further studies are needed to better evaluate this potential risk.

Glucokinase activators (GKAs)

Glucokinase, a unique isoform of the hexokinase enzymes, which plays a critical role in glucose homeostasis, was identified during the past three to four decades as a new, promising drug target for type 2 diabetes.

Glucokinase catalyzes the transfer of phosphate from ATP to glucose, generating glucose-6-phosphate. This reaction is the first, rate-limiting step in glucose metabolism (20).

Glucokinase (GK) exhibits two different actions in pancreatic islet β -cells (insulin independent) and hepatocytes (insulin independent). Glucokinase serves as a glucose sensor of the insulin producing pancreatic islet β -cells. In the liver, it controls the conversion of glucose to glycogen and regulates hepatic glucose production (21).

Diseases caused by GK gene mutations provide the best evidence regarding the importance of GK in glucose homeostasis. Activating GK mutations cause hyperinsulinemic hypoglycaemia whereas inactivating mutations cause maturity onset diabetes of the young (MODY - 2) (22).

Glucokinase activators (GKAs) increase the affinity of GK for glucose by as much as ten-fold, which in turn potentiates insulin biosynthesis and release. The published results of treating type 2 diabetic patients with GKAs for 1 week demonstrate that these agents lower blood glucose effectively in a dose-dependent manner without medically significant side effects except moderate hypoglycemia at higher doses (23). However, a recent study demonstrated that GKA (MK 0941) was associated with elevations in triglycerides and blood pressure (24).

Conclusion

Intensive research and development has succeeded in producing antidiabetic drugs with new mechanisms of action. It remains to be seen whether these new drugs withstand the test of time and secure a significant place among approved antidiabetic medications. However, it should be appreciated that the discovery of these new agents made a remarkable improvement in our understanding of glucose homeostasis with potential for further advances.

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