Colesevelam: A novel drug for comorbid diabetes and dyslipidemia

Sir,

Diabetes mellitus (DM), a multifactorial metabolic disease, affects more than 180 million people worldwide and is expected to affect approximately 360 million by 2030.[1] Type 2 DM (T2DM) accounting for around 90% of case is characterized by reduced sensitivity to insulin and decreased insulin production by pancreatic beta cells, resulting in decreased peripheral glucose uptake and increased hepatic glucose production. Currently, different types of drugs are available to help lower blood sugar in people with T2DM, each with different mechanism of action, namely, sulponylureas, biguanides, alpha-glucosidae inhibitors, thiazolidinediones, meglitinides, amylin synthetic derivatives, incretin mimetics, DPP-IV inhibitors, and insulin. Compared with patients without diabetes, those diagnosed with T2DM are at greater risk for developing primary and secondary complications, such as macrovascular and microvascular diseases. In addition to hyperglycemia, dyslipidemia and hypertension also contribute to the risk of complications in patients with T2DM. Therefore, treatment regimens for T2DM should aim to address multiple clinical features of this disease.[2]

Recently, colesevelam hydrochloride was approved by FDA in 2008 as adjunctive treatment for T2DM in combination with sulfonylurea, metformin, and/or insulin therapy.[3] Colesevelam hydrochloride is the only bile acid sequestrant that is FDA-approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It is also approved for the treatment of primary hyperlipidemia (as monotherapy or in combination with a statin).[4] In adults with T2DM, colesevelam hydrochloride reduces both low-density lipoprotein cholesterol (LDL-C) and glycated hemoglobin.

Colesevelam is a bile acid sequestrant and has a high binding capacity for bile acids in intestine. Reabsorption and enterohepatic circulation of bile acids is reduced leading to upregulation of hepatic enzyme cholesterol 7-alpha-hydroxylase, causing an increase in conversion of cholesterol to bile acids and an increase in activity of hydroxymethylglutaryl-coenzymeA (HMG-CoA) reductase. Clearence of LDL-C in blood and decreased LDL-C level in serum is seen as a result of upregulated hepatic LDL receptors.[3] The exact mechanism by which colesevelam hydrochloride lowers glucose is unknown and is currently under investigation. It may involve bile acid modulation, farnesoid X receptor/liver X receptor expression, and its downstream effects on glucose production, and/or TGR5 receptor, and its downstream effects with the release of glucagon-like peptide-1.[2,5] Emerging data suggest a partial regulatory role for FXR modulators in peripheral insulin sensitivity suggesting a future role for FXR for treating insulin resistance and T2DM.[6]

The approval was based on data from three double-blind, 26-week clinical studies, showing that add-on colesevelam therapy yielded a statistically significant reduction in mean glycated hemoglobin of 0.5% versus placebo. In addition, the add-on colesevelam therapy with metformin, sulphonylurea, and insulin also led to a statistically significant decrease of 14 mg/dl in mean fasting plasma glucose levels. In all the three studies, the addition of colesevelam yielded statistically significant 12–16% reductions in mean LDL-C levels.[7-9]

Colesevelam hydrochloride is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is neither absorbed nor metabolized systemically, with distribution limited to the gastrointestinal tract and hence does not interfere with systemic drug metabolizing enzymes such as cytochrome P-450.[6] Flatulence, dyspepsia, diarrhea, and nausea are the common side effects reported.

Colesevelam is not recommended for the treatment of T2DM and diabetic ketoacidosis and is contraindicated in persons with bowel obstruction, those with serum triglycerides level of >500 mg/dl, or with a history of hypertriglyceridemia-induced pancreatitis.[3]

The standard colesevelam hydrochloride dosing schedule is 3.75 g daily (six 625-mg tablets), given as three tablets twice daily or six tablets once daily.

Colesevelam is a new addition to the arsenal for the management of T2DM and offers a dual advantage of improving dyslipidemia with glycemic control in these patients.

Alok Dixit, Pinki Pandey[1]

Departments of Pharmacology, [1]Pathology, M M Institute of Medical Sciences and Research, M M University, Mullana, Ambala, Haryana, India

Address for correspondence:
Dr. Alok Dixit,
E-15, MMIMSR Campus, M M University, Mullana,
Ambala, Haryana, India.
E-mail: alkdxt@yahoo.co.in

References

1. Country and regional data on diabetes. Available from: http://www.who.int/diabetes/facts/world_figures/en/index.html [Last accessed on 2011 Dec 16].
2. Fonseca VA, Handelsman Y, Staels B. Colesevelam lowers glucose and lipid levels in type 2 diabetes: The clinical evidence. Diabetes Obes Metab 2010;12:384-92.
3. Sekhri K, Saha L. Colesevelam hydrochloride: A novel agent in patients with type 2 diabetes. Int J App Basic Med Res 2011;1:113-5.
4. Handelsman Y. Role of bile acid sequestrants in the treatment of type 2 diabetes. Diabetes Care 2011;34(Suppl 2):S244-50.
5. Staels B. A review of bile acid sequestrants: potential mechanism(s) for glucose lowering effects in type 2 diabetes mellitus. Postgrad Med 2009;121(Suppl 1):25-30.
6. Hasan SAA, Shobha C. Colesevelam a bile acid sequestrant use in type 2 diabetes mellitus as glucose and lipid lowering agent. Indian Journal of Pharmacy Practice 2011;4:16-22.
7. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. Diabetes Care 2008;31:1479-84.
8. Bays HE, Goldberg RB, Truitt KE, Jones MR. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. Arch Intern Med 2008;168:1975-83.
9. Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type II diabetes mellitus and inadequate glycemic control receiving insulin based therapy. Arch Intern Med 2008;168:1531-40.

Access this article online

Website: http://www.cysonline.org

DOI: 10.4103/2229-5186.103102

Quick Response Code

Author Institution Mapping (AIM)

Please note that not all the institutions may get mapped due to non-availability of the requisite information in the Google Map. For AIM of other issues, please check the Archives/Back Issues page on the journal's website.