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Review Article

BENEFICIAL EFFECTS OF INCORPORATING COLESEVELAM HYDROCHLORIDE

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ABSTRACT

Bile sequestrants have been used for almost 50 years to lower low density lipoprotein cholesterol (LDL-C). Over the past 15 years, many novel and emerging drugs have made it possible to achieve optimal glycemic control, generally in combination therapy, without untoward effects of weight gain, hypoglycemia, and other adverse effects with traditional agents. Although the long-term efficacy and safety of some of the newer classes of agents are yet to be determined, bile acid sequestrants represent a unique long-standing class of agents. Colesevelam HCl is the only drug approved for this dual indication and is an adjunct in the treatment of both hyperglycemia and hypercholesterolemia that frequently co-exist in adults with T2DM.The advent of colesevelam in 2000 provided a more tolerable add-on LDL-C-lowering agent with an excellent safety record and with likely benefit for coronary heart disease events. Colesevelam lowers LDL-C approximately 15%, and has an additive effect when combined with statin or non-statin lipid-modifying agents. It also tends to increase triglyceride levels. The discovery that bile sequestrants also lower glucose levels led to definitive large-scale clinical trials testing the effect of colesevelam as a dual antihyperglycemic agent with LDL-C-lowering properties in type 2 diabetic subjects on metformin-, sulfonylurea- or insulin-based therapy with inadequate glycemic control. Colesevelam was well tolerated, with constipation being the most common adverse effect, and did not cause weight gain or excessive hypoglycemia. Colesevelam thus combines antihyperglycemic action with LDL-C-lowering properties, and should be useful in the management of type 2 diabetes.

Keywords: colesevelam hydrochloride,hypercholesterolemia, hyperglycemia.

INTRODUCTION

Bile acid sequestrants (BASs) were one of the first classes of drugs to show that cholesterol-lowering therapy decreases the risk of cardiovascular disease (CAD). However, use of first-generation BASs such as cholestyramine and colestipol has been limited by poor tolerability and a relatively weak effect on lowering of low-density lipoprotein cholesterol (LDL-C)[1,2]. Currently, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are the first choice for treatment of hyper-LDL-cholesterolemia based on their stronger LDL-C lowering effect and prevention of cardiovascular events. However, co-administration of BASs with statins may produce lower LDL-C levels[3,4,5]. Second-generation BASs such as colesevelam (used clinically in the USA since 2000 and colestimide (also called colestilan, and used clinically in Japan since 1999 have improved tolerability. BASs also have a glucose-lowering effect, and are currently being re-evaluated for their potential use in combination with statins or antidiabetic agents[6,7].

Evidence indicates that effective treatment of hyperglycemia, and dyslipidemia ameliorates the occurrence and severity of the vascular complications of type 2 diabetes. At a time where diabetes prevalence is expanding significantly world-wide, it is critical that every effort be made to achieve recommended treatment targets for vascular risk factors as early on in the

course of diabetes as possible. The American Diabetes Association (ADA) has recommended an HbA1c target of <7.0% as the target for good glycemic control, and in individual patients, a goal as close to normal (HbA1c <6.0%) without occurrence of hypoglycemia,[7,8,9] while the American Association of Clinical Endocrinologists (AACE) has recommended an HbA1c goal of <6.5%. The primary lipid goal for people with diabetes recommended by the National Cholesterol Education Program is to achieve a LDL-C value of <100 mg/dL, and for very high-risk subjects of ≤70 mg/dL.[10] Based on the most recent surveys a large proportion of subjects with type 2 diabetes are not at their HbA1c and LDL-C goals.[11,12]

It has become abundantly clear that as glycemic and lipid treatment goals have become more stringent, a requirement for early combination therapy is needed in many patients. While this is self-evident in severely hyperglycemic patients, it is not always appreciated that the absolute glucose-lowering efficacy of a single oral antihyperglycemic agent is smaller in subjects who have milder degrees of hyperglycemia. Thus even in subjects with more modest degress of hyperglycemia, add-on treatment to monotherapy, usually metformin, is frequently required. This approach has been embodied in the recently published titration protocols developed by the ADA and the AACE for the treatment of hyperglycemia.

Similarly it is being increasingly appreciated that an LDL-C target of ≤70 mg/dL often requires ≥50% reduction in LDL-C levels, an effect that may not always be achieved with maximum doses of statin montherapy. Thus add-on treatment with secondary LDL-C-lowering agents is frequently required as well. These needs have stimulated drug development and this has led to the introduction of several new antihyperglycemic and LDL-C-lowering agents which will require long-term evaluation for safety and health efficacy. It is in this context that the recent introduction of a second generation bile sequestrant, colesevelam, as an antihyperglycemic agent with LDL-lowering properties needs to be appreciated.[13-15]

Initial use of bile acid sequestrants as LDL-C-lowering agents

Colesevelam was first introduced as an LDL-C-lowering drug in 2000. This followed the long-standing use of bile acid binding resins for treatment of hypercholesterolemia beginning almost 50 years ago.As their cholesterol-lowering properties were appreciated, the bile sequestrants became the initial choice for lowering of elevated LDL-C. The first resin available was cholestyramine, to be followed a few years later by colestipol. These are positively charged, non-absorbable, anion-exchange, long-chain polymers that bind the anionic bile acids, and in so doing disrupt the enterohepatic circulation of bile acids, depleting the bile acid pool by about 40%. Normally approximately 5% of the bile acid pool is lost daily in the stool, an amount that is replaced by new bile acid synthesis from hepatic cholesterol, initiated by the action of the rate limiting enzyme of bile acid synthesis, cholesterol 7α hydroxylase. This daily synthesis of bile acids accounts for a sizable portion of daily cholesterol turnover (about 50%) and is regulated through the action of the farnesoid X receptor (FXR) in the liver on cholesterol 7α hydroxylase. Bile acids are the primary ligand of FXR and inhibit its activity, leading to suppression of the hydroxylase. Thus bile acid sequestration will result in loss of FXR-mediated suppression of cholesterol 7α-hydroxylase, leading to a rise in its activity which diverts hepatic cholesterol to bile acid synthesis. The fall in hepatocyte cholesterol concentration then results in an upregulation of LDL receptors and a fall in circulating LDL-C levels. Cholestyramine in doses of 4 to 24 g and colestipol 2 to 16 g daily were shown to lower LDL-C in a dose-dependent manner by 5% to 28%, and in the case of colestipol, apo B was reduced in parallel by 2% to 28%.[16,17] Both agents caused a modest increase in triglyceride levels.

A major barrier to the more widespread use of these two first generation sequestrants is their unpalatable gritty consistency when the powder is ingested as slurry with liquid. In addition constipation and flatulence are common particularly with higher doses. The introduction of statins in the late 1980s,

which were both more potent as well as more tolerable than bile acid sequestrants, quickly displaced these agents as first choice treatment for lowering LDL-C. Despite this, the limitations of statin therapy in patients with severe hypercholesterolemia in whom a minimum of 50% LDL-C lowering was needed, were soon appreciated. Several studies were published in the early 1990s demonstrating the value of add-on cholestyramine or colestipol to treatment with, pravastatin,fluvastatin and lovastatin, in which approximately 50% lowering of LDL-C and up to 40% lowering of apo B was achieved. Furthermore combination of these agents with non-statin drugs such as niacin or fibrates provided added LDL-C-lowering capability to triglyceride-lowering or HDL-C-raising agents, without the safety concerns that had been raised by combined use of these drugs with statins. The large body of published clinical trials data, the record of safety, the characterization of their adverse effects, and the decades-long experience with first generation bile acid sequestrant therapy in the treatment of hypercholesterolemia are important factors in evaluating the place of colesevelam in the management of type 2 diabetes because of the similarities in pharmacology and mechanisms of action among all bile acid sequestrants.[18]

Improved Lipoprotein Particle Subclasses

A randomised, double-blind, placebo-controlled study evaluated lipid- and glucose-lowering effects ofcolesevelam in patients with prediabetes and primary hyperlipidaemia and reported the effect of colesevelam on lipoprotein particle concentration and particle size (determined by nuclear magnetic resonance spectroscopy) in these patients.

At the end of the study, mean reduction from baseline in total LDL particle concentration was significantly greater with colesevelam versus placebo (mean treatment difference: −113 nmol/L; p = 0.02). Increases in total very low-density lipoprotein particle concentration (VLDL-P) and high-density lipoprotein particle concentration (HDL-P) did not differ significantly between the groups; however, with colesevelam versus placebo, there were significantly ($p < 0.05$) greater increases in large and medium VLDL-P and large HDL-P and reductions in small VLDL-P. Mean size increases were significantly greater with colesevelam for VLDL (mean treatment difference: 5.3 nm; $p < 0.0001$) and HDL (0.1 nm; $p = 0.002$).

Colesevelam improved the overall atherogenic lipoprotein profile in adults with prediabetes and primary hyperlipidaemia, despite potentially less favourable changes in VLDL particles.[19]

Bile acid sequestrants prevent cardiovascular disease

In recent years concerns about the effects of antihyperglycemic agents on cardiovascular disease (CVD) are coming in to focus. The issue was initially raised by the University Group Diabetes Program which found that the biguanide phenformin and the sulfonylurea tolbutamide were associated with increased occurrence of cardiovascular disease.[20] This led to the withdrawal of phenformin, and the requirement for a black box warning for all sulfonylurea and subsequently meglitinide drugs. There has been little subsequent evidence that sulfonylurea drugs increase CVD, and the remaining biguanide, metformin, in a single small study was associated with a reduced occurrence of myocardial infarction.[21] However a recent meta-analysis of clinical trials using rosiglitazone has once again raised concern that some antihyperglycemic agents may have deleterious effects on CVD.[22]Because CVD is of such importance in the prognosis of type 2 diabetes, this issue has received great attention, such that the US Food and Drug Agency has recently recommended that long-term clinical trial assessments of effects of all new antihyperglycemia agents on CVD incidence will now be mandatory.[23] This requirement is also probably necessary for all lipid-lowering agents used in long-term diabetes management, as has been recently highlighted by the finding that fenofibrate did not significantly reduce the primary CVD outcome in a large population with type 2 diabetes.[24]

In this setting it is worth briefly reviewing the available evidence that bile acid depletion therapy has beneficial effects on CVD occurrence. The first indication that lowering of LDL-C through biliary diversion could successfully reduce CVD events comes from the Program on the Surgical Control of the Hyperlipidemias (POSCH).[25] In this study of 838 men and woman with hypercholesterolemia who had survived a first myocardial infarction, biliary diversion and LDL-C reduction was achieved by means of partial ileal bypass surgery. LDL-C levels were reduced by 37.7% over a 5-year period compared to that in the control group and this was accompanied by a significant 35% reduction in combined coronary heart disease (CHD) mortality and non-fatal myocardial infarction. In the modern context, this study is highly relevant because it constitutes clinical trial evidence supporting the contention that lowering of LDL-C can explain most if not all of the beneficial effect on CVD in the long-term clinical trials with statins. The strongest evidence that the effects of surgically induced biliary diversion are mirrored by sequestrant-induced biliary depletion comes from the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) and the NHLBI Type II Coronary Intervention Study. In the CPPT, one of the first large studies to definitively associate a drug-induced reduction in LDL-C with a reduction in CHD risk, 3806 men were randomized to cholestyramine or placebo for a mean of 7.4 years; the cholestyramine group had a 19% reduction in CHD risk ($p < 0.05$) that was associated with a 13% decrease in LDL-C levels.The NHLBI Type II Coronary Intervention Studyevaluated the effects of cholestyramine versus placebo on the progression of coronary angiographic lesions after 5 years of treatment in 116 patients.[26] LDL-C levels were reduced by 26% in the cholestyramine and 5% in the placebo groups ($p < 0.001$) and coronary lesions progressed in 49% of placebo-treated patients versus 32% of cholestyramine-treated patients ($p < 0.05$). There have also been several secondary intervention trials using bile acid sequestrants in combination with niacin, statins and/or fibrates which were uniformly and in some cases dramatically positive, but in which it was not possible to tease out the effect of the bile acid sequestrants from the other agents used. Finally a meta-analysis of 8 bile acid sequestrant studies found that monotherapy significantly reduced cardiac mortality. While there have been no such intervention trials with colesevelam, the evidence to date supports the notion that lowering of LDL-C through bile acid depletion is associated with beneficial effects on CHD.[27,28,29]

Colesevelam as an LDL-C-lowering agent

Although colesevelam acts in the same way as do cholestyramine and colestipol it exhibits several important differences from them. First, colesevelam was developed to have enhanced specificity, greater affinity, and higher capacity for binding bile acids than cholestyramine or colestipol. This was achieved by engineering long hydrophobic side chains to the backbone polymer, which maximize hydrophobic interactions with bile acids, adding to the effects of the ionic bonds that bind bile acids in the two first generation compounds. Thus colesevelam is at least 2 to 3 times more potent on a weight basis than either cholestyramine or colestipol. Hence smaller amounts of colesevelam can be used effectively, with less adverse effects, and with greater tolerability through its packaging into tablets instead of a slurry of liquefied powder. Although the usual dose requires taking 6 to 7 tablets (625 mg/tablet) per day, this is still considerably more acceptable than the ingestion of an insoluble powder several times a day. Finally there is no need for titration of the dose of colesevelam to allow for tolerability, unlike that commonly required by first generation sequestrants.

Monotherapy

The first of the clinical trials with colesevelam evaluating its efficacy as an LDL-C-lowering agent, utilized a double-blind, placebo-controlled, dose ranging design (1.5, 2.25, 3.0, or 3.75 g/day), conducted in 137 patients for 6 weeks. Colesevelam lowered LDL-C levels

significantly and dose-dependently by up to 19%, increased HDL-C by up to 8% to 9% and no significant changes were observed in triglyceride levels. Similar findings were obtained in a 24-week study which demonstrated that LDL-C reduction occurred within 2 weeks, was sustained over 6 months and was paralleled by up to a 12% reduction in apo B.[30,31]

Combination therapy with statins

Colesevelam has been studied in combination studies with small doses of lovastatin (10 mg), simvastatin (10 and 20 mg), and atorvastatin (10 mg), in which LDL-C levels were lowered respectively by up to 34%, 42% and 48%. Although it is usually recommended that the statin dose should be up-titrated before a second agent is added if greater LDL-C lowering is needed, actual or potential adverse statin effects may limit the dose that can be used, in which case the addition of colesevelam significantly adds to the effect of low dose statins.[32,33]

Combination therapy with non-statin drugs

Combination of colesevelam with ezetimibe may be helpful in subjects intolerant to statin treatment or in subjects who can tolerate only minimal amounts of statin. Colesevelam and ezetimibe have different modes of action and therefore might be expected to have additive effects on LDL-C. This was confirmed in several short-term studies in which the combined treatment lowered LDL-C by 30% to 40%. In combination with fenofibrate, colesevelam was shown to lower LDL-C (17%), beyond that achieved with a fibrate, while the presence of the fibrate assured that there would be net triglyceride reduction (32%). This approach with or without added ezetimibe may be useful if there was a need to avoid or minimize statin therapy in subjects with mixed dyslipidemia.[34,35]

Colesevelam, a new antihyperglycemic agent

The effect of bile sequestrants to lower glucose levels was first noted in 1994 in a study of cholestyramine in treatment of dyslipidemia in type 2 diabetes. Several subsequent studies produced conflicting results, but the Glucose Lowering Effect of Welchol study (GLOWS) clearly demonstrated that colesevelam improved glycemia in 65 type 2 diabetic subjects inadequately controlled on oral antihyperglycemic agents and randomized to 3.75 g of colesevelam versus placebo for 12 weeks.Colesevelam treatment was associated with an HbA1c reduction of 0.5% from a baseline value of 7.9% to 8.1% compared to placebo. In addition there was a reduction in those receiving colesevelam in fasting glucose at 4 and 8 weeks and postprandial glucose at 12 weeks, as well as fructosamine levels, from baseline compared to placebo. In subjects with a baseline HbA1c ≥ 8.0%, the difference between colesevelam and placebo treatment was reduced by 1.0%. These findings in this pilot study led to the larger pivotal trials for the indication of the use of colesevelam for treatment of hyperglycemia in type 2 diabetes.[36,37]

The pivotal trials testing a glucose-lowering indication for colesevelam

Three similarly designed, concurrent, prospective, multi-center, randomized, placebo-controlled parallel-group lasting 16 to 26 weeks were conducted between August 2004 and July 2006, testing the effects of colesevelam on glycemic and lipid measures in type 2 diabetic subjects inadequately controlled on sulfonylurea, metformin and insulin treatments respectively. Since these are the only large-scale clinical trials with the primary objective of assessing the antiglycemic properties of colesevelam in established type 2 diabetic subjects that have been published, they are discussed below in detail. The subjects enrolled had an HbA1c between 7.5% to 9.5%, and in the metformin and sulfonylurea studies were respectively on stable doses of either metformin or a sulfonylurea alone, or in combination with other oral antihyperglycemic agents; dipeptidyl protease IV inhibitor therapy was not included. In the insulin studies participants had to be taking insulin alone or in combination with oral agents. In all of the studies, individuals with an LDL-C < 60 mg,

a triglyceride level >500 mg/dL or with dysphagia, or swallowing or intestinal dysmotility disorders were among those excluded. Subjects were withdrawn from the study if their HbA1c or fasting glucose at any visit exceeded 10% or 260 mg/dL respectively or they developed hypoglycemia. After a 2-week, single-blind run-in period, subjects were randomized 1:1 to colesevelam taken either as six 625 mg tablets once daily or twice daily (total 3.75 g) or matching placebo (according to the preferences of the study participant), added to their prestudy antihyperglycemic treatment. In the metformin and sulfonylurea-based treatment studies, assessments were made at 6, 12, 16 and 26 weeks, whereas in the insulin-based studies, these were done at 4, 8 and 16 weeks; all were analyzed with the last observation carried forward. The primary efficacy parameter was the HbA1c change.[38,39]

Mechanisms by which bile acid sequestrants can lower glucose levels

Colesevelam may alter luminal bile acid composition and affect intestinal glucose absorption Increase intestinal release of the incretin cholecystokinin (CCK), which results in an increase in pancreatic insulin secretion Increase secretion of incretins, such as glucagon-like peptide-1 (GLP-1) Upregulate CYP7A1 and thus increase intrahepatic bile acid synthesis, but generally decrease biliary secretion of bile acids, which would theoretically decrease GLP-1 release and thus worsen glucose metabolism However, human data demonstrate that incretins such as CCK are under tonic inhibition by endogenous bile; Increase CCK release, resulting in an increase in both first-and second-phase glucose-stimulated insulin release, possibly by increasing sensitivity of pancreatic _ cells to glucose Decrease enterohepatic bile-acid pool, decrease farnesoid X receptor activity, and reduce the inhibition of oxysterol liver X receptor (LXR) activity The ensuing increased LXR activity may: Downregulate enzymes causally related to hepatic insulin resistance and glucose intolerance Suppress hepatic gluconeogenesis Improve hepatic glucose utilization and glucose uptake; Bind bile acids, which may increase HNF4_, an important transcription factor that promotes pancreatic insulin secretion May alter luminal bile acid composition and affect intestinal glucose absorption Rat studies have shown that dihydroxy bile salts normally found in bile may chronically inhibit jejunal glucose transport Rat studies have shown that chenodeoxycholic acid, ursodeoxycholic acid, or cholestyramine supplemented diets decrease ileal (but not jejunal) glucose uptake Effects of colesevelam on bile-acid composition and the potential correlation between this effect and glucose metabolism have yet to be determined.[40-46]

Effect of colesevelam in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy

Of 461 randomized subjects, 166 and 141 completed the study in the colesevelam and placebo group respectively. Their mean age was 57 years, 53% to 56% were men, a quarter were Hispanic and 10% to 15% African American, mean BMI was 33 and mean HbA1c was 8.2% to 8.3%. About one third were on sulfonylurea monotherapy, and the remainder were receiving combination therapy with metformin or in about a quarter of these, with a thiazolidinedione. At week 26 colesevelam treatment resulted in a significant least squares mean HbA1c reduction of 0.54% ($p < 0.001$) from baseline compared to the placebo group. Similar results were observed in the sulfonylurea monotherapy (-0.79%, $p < 0.001$) and sulfonylurea combination therapy subgroups (-0.42%, $p < 0.001$). In addition both fasting glucose and fructosamine levels were reduced, with fasting glucose significantly below baseline at 6 weeks. There were more subjects in the colesevelam group with a glycemic control response – defined as achievement of either a HbA1c reduction of $\geq 0.7\%$ or a ≥ 30 mg/dL fasting glucose reduction (47%) compared to the placebo group (32%). Eighteen subjects in the colesevelam group and 40 in the placebo group met discontinuation criteria. The LDL-C fell by a net 16.7% and the triglyceride level rose by a net 17.7% in the colesevelam treated group; both were significant changes. The

most common drug-related adverse event was constipation (6.1% versus 2.6% in the placebo group) and 18 subjects in the colesevelam, versus 9 in the placebo group withdrew due to a drug-related adverse event. There was no excess of hypoglycemic events or weight gain in the treatment group.[38]

Combination therapy with metformin plus colesevelam improves lipoprotein particles in patientswith early type 2 diabetes mellitus

Initial combination therapy with metformin plus colesevelam improved the atherogenic lipoprotein profile of patients with early T2DM by significantly reducing LDL-P.The combination of metforminplus colesevelam significantly reduced LDL-C (mean treatment difference: 216.3%), total cholesterol (26.1%), non–high-density lipoprotein cholesterol (28.3%), and apolipoprotein (apo) B (28.0%) and significantly increased triglycerides (median treatment difference: 18.6%) and apoA-I (mean treatment difference: 4.4%; all P ,.001). Metformin plus colesevelam significantly reduced total LDL-P (mean treatment difference: absolute change –186 nmol/L [percent change 211.7%]; both P ,.0001), largely attributable to a reduction in small LDL-P, and increased total very-low-density lipoprotein particle concentration (mean treatment difference: absolute change 6 nmol/L; P 5 .03 [percent change 8.3%; P 5 .06]) and total high-density lipoprotein particle concentration (1.0 mmol/L; P 5 .03 [4.5%; P 5 .01]) versus metformin plus placebo.[47]

Effect of colesevelam in patients with inadequately controlled type 2 diabetes on insulin-based therapy

Of 287 insulin-treated patients randomized, 231 completed the study. Demographic characteristics of participants were very similar to those in the above two studies, although they were slightly more obese (mean BMI 35) and their mean total daily insulin dose was 74 to 78 units. Insulin therapy consisted of either basal insulin alone, insulin mixtures or true basal/bolus therapy, and about 40% were on insulin monotherapy. Over half of those on insulin/oral agent combination treatment received metformin, about a third of these subjects were treated with sulfonylurea, and just under a third were on a thiazolidinedione. The net treatment difference in HbA1c level from baseline to week 16 in the colesevelam group was -0.50% versus the placebo ($p < 0.001$); the effects were similar in those on insulin monotherapy (-0.59%) versus those treated with insulin/oral agent combinations (-0.44%) and were greater in those with a baseline HbA1c $\geq 8.0\%$ versus <8.0% (-0.57% compared to -0.38%). As in the previous studies, fasting glucose and fructosamine fell rapidly and were significantly reduced compared to placebo within 4 weeks, and there were more subjects with a glycemic control response in the colesevelam group (49%) versus placebo (32%). In this study discontinuations for hyperglycemia were similar in the two groups. The LDL-C was reduced by a net 12.8% ($p < 0.001$), apo B by a net 5.3% ($p < 0.04$) and triglyceride values increased by 21.5% (baseline triglyceride 155–167 mg/dL, $p < 0.001$). In the colesevelam-treated group, the most frequently reported drug-related adverse events were constipation (6.8%), dyspepsia (3.4%), hypoglycemia (3.4%), flatulence (2.0%), and nausea (1.4%), whereas in the placebo group, the most frequently reported adverse event was hypoglycemia (5.7%). Five subjects in the colesevelam group withdrew because of a drug related adverse effect versus 2 in the placebo group and there was no weight gain in either group.[48]

Effects of on Biomarkers of Inflammation

Statins and fibrates have been shown to lower hs-CRP levels, a paucity of data is available on the effect of bile acid sequestrants on hs-CRP levels. Results from placebo-controlled, randomized, double-blind trial have demonstrated the novel finding that colesevelam HCl therapy, in addition to decreasing LDL cholesterol levels, results in a significant reduction in hs-CRP levels. Also with studies of statins,11–13 no correlation was found between the reduction in LDL cholesterol levels and hs-CRP levels with colesevelam

HCl therapy. It is important to note that the cholesterol absorption inhibitor, ezetimibe, has been shown to lower hs-CRP levels only in combination with statins but not as monotherapy.The circulating levels of other biomarkers of inflammation, such as IL-6 and TNF- was also examined, but found no significant changes in the systemic levels of these cytokines, probably because of their short half-life. It was hypothesized that the interruption of bile acids results in reduced enterohepatic inflammatory signals, which in turn results in the decrease in hs-CRP levels with colesevelam HCl therapy.[49]

Interactions with other drugs

Although bile sequestrants are not absorbed and therefore will not influence hepatic metabolism of other drugs, they are positively charged resins and tend to bind to acidic drugs, interfering with their absorption. This effect is greatest with cholestyramine, less with colestipol and least with colesevelam. For example, no significant effects of colesevelam administration were found on the pharmocokinetics of six drugs with narrow therapeutic indices, whose absorption is interfered with by cholestyramine, namely valproic acid, digoxin, quinidine, verapamil, metoprolol and warfarin. Furthermore no effects of coadministration of colesevelam on drug levels of lovastatin, fenofibrate, metformin, glipizide, repaglinide and pioglitazone have been found. Colesevelam does interfere with absorption of glyburide, levothyroxine, oral contraceptives, and post-marketing reports suggest interactions with the therapeutic efficacy of phenytoin and warfarin. It is recommended that coadministration of colesevelam with drugs with narrow therapeutic indices, and fat-soluble vitamins be avoided; instead the administration of the sequestrant should be delayed by at least 4 hours after these medications are ingested.[50,51]

Safety in Pediatric Subjects Safety in Pediatric Subjects

A randomized, double-blind, 41-site study in 194 children aged 10 to 17 years (inclusive) with heFH (statin-naïve or on a stable statin regimen). After a 4-week stabilization period (period I), subjects were randomized 1:1:1 to placebo, colesevelam 1.875 g/d, or colesevelam 3.75 g/d for 8 weeks (period II). All then received open-label colesevelam 3.75 g/d for 18 weeks (period III), with follow-up 2 weeks later. The primary endpoint was percent change in low-density lipoprotein (LDL)-cholesterol from baseline to week 8. Secondary endpoints includedpercent change in other lipoprotein variables, including non-high-density lipoprotein (non-HDL)-cholesterol. Adverse events were also evaluated. At week 8, a significant difference from baseline in LDL-cholesterol was reported with colesevelam 1.875 g/d (_6.3%; P = .031) and colesevelam 3.75 g/d (_12.5%; P < .001) compared with placebo. Significant treatment effects were also reported for total cholesterol (_7.4%), non-HDL-cholesterol (_10.9%), HDL-cholesterol (+6.1%), apolipoprotein A-I (+6.9%), and apolipoprotein B (_8.3%) and a nonsignificant effect for triglycerides (+5.1%) with colesevelam 3.75 g/d compared with placebo at week 8. These treatment effects were maintained during period III.[52]

Perspectives on the utility of colesevelam as an antihyperglycemic agent in type 2 diabetes

The three pivotal studies demonstrate that add-on colesevelam lowers the HbA1c by about 0.5% in subjects with an average HbA1c of approximately 8.2% to 8.3%, irrespective of whether the underlying treatment is metformin-, sulfonylurea-, or insulin-based. These findings suggest that the antihyperglycemic effect of colesevelam is independent of the nature of the medication to which it is added. This would further imply that the mechanism of the antihyperglycemic effect of colesevelam is additive to those of metformin or sulfonylureas and does not appear to enhance insulin action based on surrogate markers, although more definitive studies are needed to examine this question. The mechanism by which bile sequestrants in general and colesevelam in particular improve hyperglycemia is unknown. Sequestrants may interfere with intestinal glucose absorption, potentially enhance insulin release, and experimentally through

the reduction of FXR activity, alter hepatic glucose metabolism, although studies have yielded conflicting results. Based on effects of colesevelam treatment on fasting glucose and fructosamine levels, its antihyperglycemic effect is complete within 4 weeks.

Colesevelam offers several advantages in subjects on oral antihyperglycemic therapy or insulin treatment whose HbA1c and/or LDL-C are mildly or moderately elevated above their targets. First this treatment simultaneously lowered HbA1c and LDL-C toward therapeutic targets without causing weight gain or excessive hypoglycemia in the clinical trials. Second, this class of non-absorbable resins offers a good safety record. Thirdly both surgical and pharmacologic biliary diversion to lower LDL-C has been shown to reduce coronary atherosclerosis and coronary heart disease events. Dividing the dose into 3 tablets at the midday meal and 3 at the evening meal may offer the most convenient way to administer this relatively bulky medication. This regimen also avoids interactions with most other medications which are usually taken in the morning, since their absorption should be complete by the midday meal. Finally in an era where prevention of diabetes has been accepted as an important approach to ameliorating the epidemic of diabetes including the early initiation of pharmacotherapy in high risk prediabetic individuals, colesevelam would seem to offer several advantages, for the reasons discussed above.[53-56]

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