**Introduction**

Colesevelam (Cholestagel) is an intestinal bile acid sequestrant (BAS). BAS drugs were one of the first drug classes developed for the treatment of dyslipidaemia and include colestyramine and colestipol. They were also one of the first drugs to show improvement in cardiovascular outcomes. Colesevelam is a third generation BAS, developed with a higher affinity for bile acids and fewer side effects. It has also been noted to reduce serum glucose values and produces a reduction in HbA1c of approximately 0.5%. Colesevelam may therefore be of use in patients with type 2 diabetes who require second-line treatment for dyslipidaemia or who are intolerant of statin medications.

**Pharmacology**

Bile acids are synthesised in the liver, stored in the gallbladder and then secreted into the small intestine. They then bind to fats and fat soluble vitamins, aiding their active absorption into the systemic circulation. Ninety-five percent of bile acids are returned via the enterohpatic portal system to the liver and then re-used. BASs bind bile acids in the intestine (see Figure 1) preventing their reabsorption. The bile acids are then excreted in the faeces. This causes an upregulation of cholesterol 7α-hydroxylase enzyme which increases the production of bile acids from its precursor, cholesterol. Due to this effect, the activity of HMG coenzyme A reductase is upregulated and there is increased hepatic expression of low density lipoprotein (LDL) receptors. This results in an increased clearance of LDL cholesterol (LDL-C) from the blood.

Colesevelam was noted to lower serum glucose values as a chance finding when its lipid lowering effects were being studied in clinical trials (a similar effect had been noted with colestyramine in 1994). The exact mechanism of this continues to be studied. Various mechanisms have been proposed including: decreased glucose absorption, altered gastrointestinal transit time and upregulation of farnesoid X receptors (a bile acid activated nuclear receptor). A recent multicentre, randomised controlled study designed to determine this mechanism was carried out.
out.² Sixty patients with type 2 diabetes on metformin and/or a sulphonylurea were randomised to colesvelam or placebo for three months. Factors assessed included HbA₁c, fasting and postprandial glucose, GLP-1 and GIP levels. Glucose, lipid and bile acid pathways were assessed pre- and post-therapy using stable isotope techniques.

The stable isotope studies demonstrated increased plasma glucose clearance and increased glycolytic disposal. Colesvelam was shown to increase GLP-1 and GIP secretion. It appeared to suppress endogenous glucose production and fasting glycogenolysis (although this did not reach statistical significance). Interestingly, colesvelam did not affect the absorption of oral glucose and there was no effect on gluconeogenesis. As expected, it increased cholesterol synthesis and the proportion of bile acids produced from newly synthesised cholesterol.

Colesvelam is generally safe and well tolerated. In trial subjects there was a withdrawal rate of 5–8% compared with 2.5–4% in the placebo groups. Most side effects were mild to moderate. The most common side effects were constipation (6.8%), dyspepsia and abdominal pain. The risk of hypoglycaemia is low and there were no severe episodes reported.³⁻⁵ In a trial of patients already on metformin, there was one mild hypoglycaemia event noted.⁶ In the sulphonylurea (SU) trial, there was a 1.8% increased hypoglycaemia incidence compared to placebo⁷ and, in the insulin trial, the hypoglycaemia rate was greater in the placebo group.⁸ Colesvelam is known to increase triglyceride levels by approximately 5–20%,²⁻⁴ and its use is not advised in patients with moderate to severe hypertriglyceridaemia.

One of the disadvantages of colesvelam use is that it interacts with other medications in the gut affecting their absorption. As a result, other medications should be taken 4 hours before or after colesvelam use. Colesvelam is known to interfere with the absorption of glibenclamide, phenytoin, ciclosporin, ethinylestradiol and levethoxine. There is a risk of decreased absorption of fat soluble vitamins due to the nature of colesvelam’s action. In prolonged use, vitamin supplements may be required.

**Trials of safety and efficacy**

An early study published in 1984 showed a reduction in cardiovascular (CV) endpoints with the use of the BAS colestyramine.¹ A total of 3806 asymptomatic, middle-aged men with primary hypercholesterolaemia were randomised either to treatment with colestyramine or placebo. After a mean of 7.4 years' follow up, a reduction in CV death of 24% and a 19% reduction in non-fatal myocardial infarction were revealed.

Colesvelam was initially trialled in patients with primary hypercholesterolaemia without diabetes.⁶ It was found to lower mean LDL-C by 9–18% in a 24-week trial involving 494 patients. Total cholesterol levels decreased by 4–10% and high density lipoprotein (HDL-C) levels increased by 3–4%. Triglyceride levels were noted to increase by 5–10% in the treatment groups and by 5% in the placebo group. No specific trials have evaluated colesvelam and CV endpoints.

**Specific evidence for use in diabetes**

Colesvelam’s actions have been evaluated in patients with type 2 diabetes. An initial pilot study (WelChol study) randomised 65 patients into either treatment with colesvelam or placebo. Patients had type 2 diabetes inadequately controlled on metformin and/or sulphonylurea. After 3 months, a difference in HbA₁c of 0.5% was noted between the treatment and placebo groups. The treatment group also had decreased postprandial glucose levels, a reduction in LDL-C of 11.7% and decreased total cholesterol of 7.3% compared with placebo.

Randomised controlled trials in patients already on metformin, SUs or insulin have confirmed a modest but clinically useful improvement in HbA₁c of approximately 0.5% against placebo.³⁻⁵ Fast plasma glucose was decreased by approximately 0.8mmol/L.³⁴ In a head-to-head study, patients randomised to treatment with sitagliptin observed a 0.4% improvement in HbA₁c compared with 0.3% with colesvelam.⁷ LDL-C was decreased by 12.8–16.7% in the three studies adding colesvelam to metformin, SU or insulin. Total cholesterol was decreased by 3.7–7.2%. There was no significant weight change noted and colesvelam is therefore a weight neutral treatment.³⁻⁵

**Discussion**

Treatment of both dyslipidaemia and hyperglycaemia is important in patients with type 2 diabetes to prevent CV events. Statin medications have a firm evidence base in the treatment of dyslipidaemia and are therefore included as first-line agents in national guidance. In patients requiring add-on therapy or who are intolerant of statins, colesvelam could prove a useful adjunct. Colesvelam is licensed for the treatment of primary hypercholesterolaemia and has the added benefit of reducing HbA₁c by 0.5%. It has been shown to effectively treat dyslipidaemia by decreasing LDL-C by approximately 15–20% and is also weight neutral. Its side effects and drug interactions (particularly the effect on absorption of other medications) should be borne in mind. Colesvelam is therefore a medication which diabetologists may effectively utilise in their armamentarium as an adjunct to lipid lowering therapy in patients with diabetes.

**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available online at www.practicaldiabetes.com.
References