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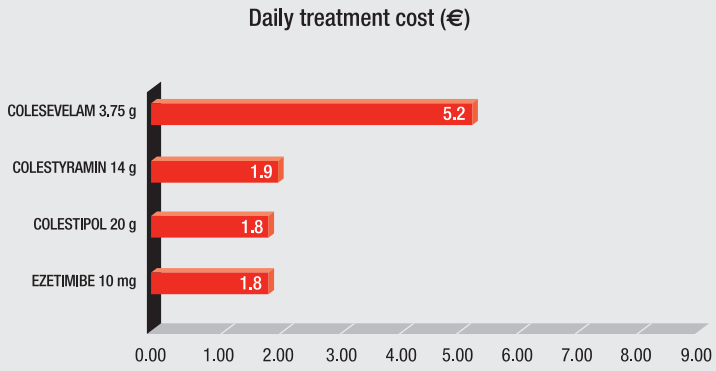
Colesevelam▲ (Cholestagel®) in primary hypercholesterolaemia

Resins are back at a much higher cost



One more resin, but with no comparison to the former resins and with no results on morbidity and mortality

- Colesevelam is a lipid lowering drug belonging to the bile acid anion-exchange resins group.
- There are no trials with results on morbidity and mortality and this drug has not been compared directly with colestyramine and colestipol, although by indirect comparisons, it does not appear to present advantages with regard to efficacy and safety.
- In monotherapy, it reduces LDL-c by 15-18%, while colestyramine and colestipol reduce LDL-c by an average of 15-30%. As adjunct therapy to other lipid lowering drugs, it produces an additional reduction of 8-16% of LDL-c.
- The most frequent adverse effects are of gastrointestinal origin just like other resins.

Therapeutic indications[1]

Colesevelam co-administered with a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) is indicated as adjunctive therapy to diet to provide an additive reduction in low-density lipoprotein cholesterol (LDL-c) levels in adult patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone. Colesevelam as monotherapy is indicated as adjunctive therapy to diet for reduction of elevated total-cholesterol and LDL-c in adult patients with primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well-tolerated.

Colesevelam can also be used in combination with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia.

Mechanism of accion and pharmacokinetics[1,2]

Colesevelam is a drug that fixes bile acids in the intestine by blocking their reabsorption. This produces an increase in the conversion of cholesterol into bile acids, HMG-CoA reductase activity and the number of liver LDL receptors, ultimately producing a reduction of LDL-c in serum.

It is not absorbed in the digestive system, and plasmatic levels are not expected to be found.

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

Posology and method of administration[1]

Combined therapy with statins, with or without ezetimibe. These drugs can be administered simultaneously or separately. *Recommended dose:* 4-6 tablets once or twice daily with food. *Maximum dose*: 6 tablets daily (3.75 g/d).

Monotherapy. *Initial recommended dose*: 6 tablets daily, once or twice daily. *Maximum dose*: 7 tablets daily (4.38 g/d).

Clinical efficacy

Twelve randomized clinical trials have been published comparing the efficacy of colesevelam with placebo in patients with mild to moderate hypercholesterolemia, either in monotherapy[3,4] or in combined therapy with statins[5-8], ezetimibe[9,10] statin+ezetimibe[11], or fibrates[12].

All these trials present limitations. The primary endpoint has been a surrogate variable (LDL-c reduction) and all the trials are short term (4-6 weeks) except one of 24 weeks[4], thus most of them not complying with the criteria established by the EMA (minimum of 12 weeks)[13]. There are no trials with results in morbidity or mortality. In combined therapy, with the exception of one trial, it was not clear that the population included were inadequately controlled statins at maximum doses, or that patients showed intolerance to statins since these were not inclusion criteria in the trials.

Monotherapy. Colesevelam (3.8-4.5 g/d) reduces LDL-c by 15-18%. The objective of reducing LDL-c down to 120 mg/dL (3.1 mmol/L) was not reached in the majority of patients. There was an increase in triglycerides in all groups with a maximum of 17%.

Combined therapy. The trials were very short and of small size, with 17-39 patients in each treatment group. The colesevelam+statin combination was more effective in reducing LDL-c than each of the components separately at the same doses, but not more effective than atorvastatin 80 mg/d[7]. The additive effect of colesevelam (2.3-3.8 mg/d) on the statin in the reduction of LDL-c was 8-16%. The additon of colesevelam to ezetimibe produced an additonal reduction of LDL-c of 11%. The addition of colesevelam to the combination of a statin at the maximum tolerated dose and ezetimibe produced a further reduction of LDL-c levels by 11%.

There are no trials comparing the efficacy of colesevelam with other resins available (colestipol and colestyramine). According to the EMA s[2] report, colesevelam 3.8-4.5 mg/d produces average reductions in LDL-c of a little more than 15%, while the maximum approved doses of colestyramine (24 g/d) and colestipol (30 g/d) reduce LDL-c by 15-30%.

Safety

Adverse reactions

The main adverse effects are of gastrointestinal origin, given that colesevelam is not absorbed. In the RCTs, the most frequent adverse effects were: flatulence (11%), constipation (10%), dyspepsia (6%), nausea and diarrhoea (3%)[15]. Only constipation and dyspepsia were reported in a higher percentage with respect to placebo. The increase in triglycerides and headache were also reported as frequent (1-10)[1].

Precautions and contraindications

It is contraindicated in intestinal and biliary occlusion.

Before starting treatment with colesevelam, secondary causes of hypercholesterolemia should de ruled out and treated.

The safety profile and efficacy of colesevelam has not been established in patients with triglyceride levels over 300 mg/dL (3.4 mmol/L), disphagia, eating disorders, severe disorders affecting gastrointestinal motility, intestinal inflammatory disease, liver impairment or major abdominal surgery.

It can provoke or worsen constipation. The risk of constipation should be weighed in patients with coronary disease and angina.

Precaution should be taken when treating patients sensitive to vitamin K or with deficits of liposoluble vitamins, such as those that suffer from malabsorption. In these cases, monitoring of the levels of vitamin A, D and E is necessary and the state of vitamin K by coagulation parameters should be obtained and corrected by vitamin supplements if necessary.

Interactions[1]

Colesevelam can affect the bioavailability of other drugs. Therefore, when the exclusion of an interaction with a drug given concomitantly cannot be made, and when small variations at therapeutic levels can be clinically important, then coleselevelam should be taken at least four hours after the other drug to reduce the risk of a reduction in absorption of that concomitant drug.

Captors of bile acids reduce the absorption of vitamin K, and therefore increase the anticoagulant effect of warfarin.

Colesevelam should be given at least four hours after levothyroxine, oral contraceptives, and ciclosporin. Close monitoring of ciclosporin plasma levels is recommended.

Use in special situations[1]

Pregnancy and Lactation: no clinical data is available on the use of this drug in these situations. **Elderly:** no dose adjustments are required. **Children under 18 years:** not authorized. **Liver impairment:** the saftey profile has not been established in this situation.

Place in therapeutics

Statins are the elective management option for the treatment of hypercholesterolemia because it has been shown that they reduce the cardiovascular morbimortality in secondary prevention and morbidity in primary prevention. Other management options that have shown efficacy in the reduction of cardiovascular morbidity and mortality are colestyramine and fibrates. Colesevelam has not been compared to colestyramine or fibrates, although by indirect comparisons, it does not appear to present any advantages with respect to any of these other drugs with regard to the reduction of LDL-c.

Colesevelam has up to now shown to be effective through a surrogate variable in the prediction of cardiovascular risk (reduction of LDL-c). Nevertheless, it is necessary to have results of morbidity and mortality to decide on the suitability of initiating treatment, especially when dealing with preventive measures that are addresed to a large group of the population.

With regard to safety, colesevelam seems to have a minor incidence of adverse gastrointestinal effects when compared to the rest of the resins, although there are doubts that this better tolerance is real when employing equipotential doses[2].

No directly comparative trials are available between colesevelam and any other drug of the same group. In any case, it does not seem to present any advantages with regard to efficacy and safety. Therefore, in the case of the need of a resin, it is more adequate to select colestyramine, which has shown a reduction in cardiovascular morbidity and mortality in patients with hypercholesterolemia.

Presentations

Cholestagel® (Genzyme S.L.) 625 mg 180 tablets (156.95 €). Requires special authorization.

References

A full report on colesevelam is available at: http://www.dtb.navarra.es

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