Cilostazol in Treating Intermittent Claudication

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Summary and conclusions

SBU's appraisal of the evidence

Intermittent claudication (cladicatio intermittens) is a symptom of atherosclerosis. The disorder causes pain in the muscles of the legs while walking, and pain subsides after a few moments of rest.

- In patients with intermittent claudication, cilostazol enables some extension in the maximum walking distance (when pain prevents further walking) compared to placebo. No studies have reported follow-up beyond 6 months.
- The effects of cilostazol in relation to smoking cessation and supervised walking exercise have not been studied. Studies have not reported whether the control groups have been helped by smoking cessation and supervised walking exercise. No studies have investigated whether cilostazol can improve the results in patients that have received such help.
- Side effects such as headache and gastrointestinal symptoms are more common with cilostazol treatment than with placebo. The studies are not designed to be large enough to enable an assessment of risk for serious and uncommon side effects.
- The scientific evidence is insufficient to determine whether cilostazol treatment for intermittent claudication is cost-effective.

Target group and technology

Intermittent claudication is a common disorder in the elderly. Approximately 5% of the population that reaches retirement age contracts the disease. Smoking is an important and modifiable risk factor. Hence, smoking cessation is essential, not least to improve survival.

The disorder's severity and course vary widely between individuals. Severe symptoms that limit mobility can lead to substantial social disability. For serious cases, and in patients who have started to feel pain even during rest (critical ischemia), various invasive treatment options may be considered, eg, open surgery or endovascular treatment of the obstructed blood vessel.

Several different treatment methods have been tested. Cilostazol inhibits an enzyme that reduces the degradation of cyclic AMP, a substance found in platelets and vessel walls. This causes the vessels to dilate, and inhibits the aggregation of platelets. Cilostazol has been approved for use in Sweden since 2007 to extend the maximum walking distance, and the pain-free walking distance, in patients with intermittent claudication who do not experience pain at rest and do not show signs of peripheral tissue damage.

Primary questions

- Does cilostazol improve walking distance in patients with intermittent claudication?
- What are the side effects and risks of treatment with cilostazol?
- What does treatment cost? Is it cost-effective?

Patient benefit

❑ In patients with intermittent claudication, cilostazol extends the maximum walking distance (when pain prevents further walking) by an average of 50 meters compared to placebo (Evidence Grade 1)*. Pretreatment walking distance was 100 to 250 meters in the different studies. No studies have reported follow-up beyond 6 months.

❑ Cilostazol's effect in relation to smoking cessation and supervised walking exercise has not been studied. Hence, it is not possible to determine whether the effects of cilostazol differ from the effects of smoking cessation and supervised walking exercise (Insufficient Scientific Evidence)*.

- Side effects such as headache and gastrointestinal symptoms are more common in treatment with cilostazol than with placebo (Evidence Grade 3)*. The studies are not designed to be large enough to enable an assessment of risk for serious and uncommon side effects. Randomized trials including approximately 1600 patients in total have not reported serious side effects.

Results from 6 randomized controlled trials show that treatment with cilostazol 100 mg twice per day extends both the initial walking distance (when pain first appears) and the maximum walking distance (when pain prevents further walking) in patients with intermittent claudication. The primary end point in the studies was walking distance (measured on a treadmill). A meta-analysis estimates that the initial walking distance is extended, on average, just over 30 meters and the maximum walking distance by approximately 50 meters in treatment with cilostazol compared to placebo. The studies do not report whether the participants received advice on lifestyle changes and were challenged to increase physical activity, stop smoking, or change their diet. The studies did not allow concurrent treatment with platelet inhibitors and do not report on how many participants received lipid-lowering therapy. All studies were conducted in patients above 40 years of age with stable intermittent claudication, ie, a verified diagnosis and no change in their condition for at least 6 months.

Side effects in the gastrointestinal tract and headache are relatively common. The studies are not designed to be large enough to enable an assessment of risk for serious and uncommon side effects. Available randomized studies totaling approximately 1600 patients have, however, not reported serious side effects. Because of the mechanism of action, patients with heart failure were not included in the studies. Heart failure is also designated as a contraindication.

Available studies suggest that cilostazol enables some increase in walking distance in patients with intermittent claudication. The effects appear after a few weeks and are shown to continue up to 6 months. The scientific evidence is insufficient to determine whether the effects help improve the quality of life for patients. The effects have not been studied in relation to other treatments that have demonstrated effects, eg, supervised walking exercise.

Ethical aspects

The fact that a drug is available to treat intermittent claudication should not lead to prescribing pharmacotherapy without first informing the patient about the importance of smoking cessation and exercise. The randomized trials do not always report on how active the subjects were in regard to these measures. For instance, the studies do not specify the interventions that the control groups received as regards smoking and optimum exercise options.

Economic aspects

- The scientific evidence is insufficient* to draw conclusions about the cost-effectiveness of cilostazol treatment in patients with intermittent claudication.

The pharmaceutical cost in cilostazol (Pletal) treatment is approximately 17 Swedish kronor (SEK) per patient and day, at a dose of 100 mg twice per day. The drug is included (as of April 22, 2008) in the pharmaceutical reimbursement system. According to the manufacturer, approximately 2500 patients could be eligible for treatment with Pletal based on current indications. This would mean that the total annual cost for the drug in Sweden would be somewhat over SEK 15 million. During the first half of 2009 approximately 1000 packets were sold, corresponding to an annual cost just over SEK 1.6 million.

We identified only one economic evaluation study of cilostazol treatment in patients with intermittent claudication. The scientific evidence is insufficient for conclusions on its cost-effectiveness.

The Dental and Pharmaceutical Benefits Agency (formerly called the Pharmaceutical Benefits Board) decided to include Pletal in the reimbursement system based on the economic analysis presented by the manufacturer, which compared Pletal to placebo. The cost per quality-adjusted life-year (QALY) was estimated at approximately SEK 230 000 (in 2008).

*** Criteria for evidence grading SBU's conclusions**

Evidence Grade 1 – Strong Scientific Evidence. The conclusion is corroborated by at least two independent studies with high quality, or a good systematic overview.
Evidence Grade 2 – Moderately Strong Scientific Evidence. The conclusion is corroborated by one study with high quality, and at least two studies with medium quality.
Evidence Grade 3 – Limited Scientific Evidence. The conclusion is corroborated by at least two studies with medium quality.
Insufficient Scientific Evidence – No conclusions can be drawn when there are not any studies that meet the criteria for quality.
Contradictory Scientific Evidence – No conclusions can be drawn when there are studies with the same quality whose findings contradict each other.

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The complete report is available in Swedish.