Peripheral edema and headache associated with amlodipine treatment: a meta-analysis of randomized, placebo-controlled trials

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Background: Use of amlodipine for treatment of arterial hypertension (AH) and stable angina pectoris (SAP) is sometimes limited by occurrence of peripheral edema and headache.

Purpose: As these side effects (SE) occur also on placebo in clinical trials, we aimed to explore the true magnitude of this phenomenon by determining the rate and placebo-adjusted rate of these SE.

Methods: We performed a meta-analysis by including all randomized, placebo-controlled trials reporting edema and headache with amlodipine in patients with AH and SAP. Placebo-adjusted rate (%) was determined as follows: (SE amlodipine % - SE placebo %) / SE amlodipine %. Electronic databases PubMed, Web of Science, and Cochrane library were systematically searched for eligible trials published until July 2018. Diseases such as heart failure, severe renal or hepatic disease were not considered. Furthermore, in most of the trials, a wash-out period took place before the study medication was given.

Results: Data from 7,226 patients of 22 trials were analyzed. In most of the analyzed trials, duration of follow up was comparable, and lasted about 8 weeks. All studies were graded as high quality according to Jadad score. Rate of edema was higher on amlodipine compared with placebo (16.6 vs 6.2%, RR: 2.9, 95% CI: 2.5-3.36, p<0.0001). The placebo-adjusted rate was 63%, indicating that 37% of edema cases were unrelated to amlodipine. Treatment with low/medium doses (2.5-5 mg) resulted in lower rates of edema (RR: 2.01, 95% CI: 1.41-2.88, p=0.0001) compared with high dose (10 mg) (RR: 3.08, 95% CI 2.62-3.6, p=0.0001, p for interaction=0.03). For each 5-mmHg reduction in BP one could expect lower rates of edema using a low/medium compared with high dose of amlodipine (3.2 vs. 12.2%). Headache was reduced using amlodipine compared with placebo (7.9 vs 10.9%, RR: 0.77, 95% CI: 0.65-0.90, p=0.002) and was driven by use of low/medium doses (RR: 0.52, 95% CI: 0.40-0.69, p=0.00001 versus RR: 0.92, 95%-CI: 0.74-1.15, p=0.45, for high doses, p for interaction =0.002). According to a data from six studies administration of renin-angiotensin-inhibitors as add-on therapy to low/medium dose of amlodipine, resulted in higher BP reduction with equivalent rates of edema compared with low/medium dose of amlodipine (p for interaction =0.23), which may be advantageous in obtaining guideline-recommended target BP values. Conclusion: Patients on amlodipine exhibit a dose-dependent 3-fold increased risk of peripheral edema compared with placebo. Of note, up to one third of edema cases on amlodipine might not be induced by amlodipine. Headache is reduced on amlodipine treatment, mainly driven by use of this drug at low/medium doses potentially related to better blood pressure control. Amlodipine used at appropriate doses express the best risk-benefit ratio concerning edema and prevention of headache, thus maintaining treatment adherence, alone or in combination with other drugs.