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Amlodipin + atorvastatin▲ (Caduet®, Astucor®)

A combination that makes no sense

[-] 0 INSUFFICIENT EVIDENCE | **1 NO THERAPEUTIC INNOVATION** | 2 SOME ADDED VALUE IN SPECIFIC SITUATIONS | 3 MODEST THERAPEUTIC INNOVATION | 4 IMPORTANT THERAPEUTIC INNOVATION [+]

Therapeutic indications[1]

This combination is indicated in the prevention of cardiovascular events in patients with hypertension, who have three other concomitant cardiovascular risk factors, with normal or mildly elevated cholesterol, and with no clinical evidence of coronary disease. This combination is indicated when the use of amlodipin and low dose atorvastatin is considered adequate according to the current management guidelines. It should be employed when the response to diet and other non-pharmacological measures has not proven effective.

Mechanism of action and pharmacokinetics[2,3]

Please refer to the EMEA Product Information for amlodipin and atorvastatin.

Posology and method of administration[1]

This drug combination (A/A) is administered orally. The initial starting dose is 5 mg amlodipin/10 mg atorvastatin once daily. This dose can be increased to 10/10 mg daily. The dose can be taken at any time during the day irrespective of meal times. It can be employed solely or in combination with other anti-hypertensive agents, but it should not be employed with calcium channel antagonists or with any another statin. Concomitant use of A/A with fibrates should be avoided.

- **The combination of amlodipin-atorvastatin (A/A) is indicated in the prevention of cardiovascular events in hypertensive patients with three other concomitant risk factors, and with normal or mildly elevated cholesterol levels.**
- **The efficacy of statins to reduce cardiovascular risk in primary prevention in patients with normal cholesterol levels has not been sufficiently demonstrated.**
- **The addition of atorvastatin in patients under treatment with amlodipin in the indication mentioned increases the risk of adverse reactions and the cost of treatment with no clear health benefits. Therefore this combination is not justified.**

The prescription of statins in primary prevention is not justified without taking into account the lipid profile.

Clinical efficacy

The authorized indication for the A/A combination at fixed doses originates from the ASCOT-LLA trial. However, there is more evidence with respect to the role of the addition of statins (pravastatin) in the management of patients with hypertension with moderately high levels of cholesterol like the ALLHAT-LLT trial. There is also information on the role of the addition of atorvastatin in the management of diabetes patients with high cardiovascular risk that have a normal cholesterol profile (CARDS and ASPEN trials).

The ASCOT-LLA[4] trial evaluates the efficacy of A/A combination with respect to placebo in the prevention of non-fatal infarction and fatal coronary disease in hypertensive patients with cholesterol levels ≤ 250 mg/dL (or 6.5 mmol/L), and at least, three other cardiovascular risk factors. The study included 10,305 patients with hypertension and with an average age of 63 years, of which 19% were women. The expected duration was 5 years, but the study was suspended earlier after a follow-up of 3.3 years.

The patients under treatment with A/A presented a lower incidence in the primary endpoint (6.0 vs 9.4 cases/1,000 patients-year), that is a reduction in absolute risk (ARR) of 3-4 cases/1,000 patients-year. This means that the proportion of patients that did not present either a non-fatal myocardial infarction or fatal coronary disease during the study period was 93.3%, and after the addition of atorvastatin for 3.3 years, the percentage reached 86.4% (NNT = 94 patients for 3.3 years).

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.

Adverse reactions[2,3]

FRECUENCY	AMLODIPIN	ATORVASTATIN
Common 1-10%	Somnolence, dizziness,headache, palpitations, rubefaction, abdominal pain, nausea, oedema, peripheral oedema, fatigue.	Insomnia, dizziness, headache, hypoesthaesia, paresthaesia, abdominal pain, nausea, dyspepsia, diarrhoea, constipation, flatulence, pruritus, skin rash, arthralgia, myalgia, back pain, chest pain, asthenia, increments in GPT, GOT and CPK.
Rare 0.1-1%	Increase or loss in weight , insomnia, mood changes, tremor, hypoesthaesia, paraesthaesia, vision disorders, tinnitus, syncope, hypotension, disnea, rhinitis, vomiting, dyspepsia, alterations in bowel habits, dry mouth, alterations in taste , alopecia, purpura, skin colour loss, sweating, pruritus, skin rash, arthralgia, myalgia, muscle cramps, back pain, urine alterations, nicturia, decrease in micturation intervals, impotence, gynecomastia, chest pain, asthenia, pain, general malaise.	Thrombocytopenia, alergic reactions (urticaria), hyperglycaemia, weight increase, hypoglycaemia, anorexia, peripheral neuropathy, amnesia, tinnitus, vomiting, alopecia, impotence, general malaise.

The ALLHAT-LLT[5] trial evaluated the effects on mortality by adding pravastatin 40 mg daily to the management regimen of patients with hypertension and with at least one additional cardiovascular risk factor and moderately elevated levels of cholesterol. The mean follow-up period was 4.8 years and the study included 10,355 patients, of which 50% were women. No benefits were found either in the primary endpoint (total mortality) or in the secondary endpoints.

The CARDS[6] and ASPEN[7] trials was carried out on diabetes patients with other cardiovascular risk factors and consisted in the administration of atorvastatin 10 mg daily or placebo despite the patients presenting normal cholesterol levels. There was an important proportion of patients with hypertension (CARDS, 84%; ASPEN, 55%). The primary composite endpoint included acute coronary disease, revascularization, or stroke (CARDS). In the ASPEN study, within the combined endpoint, death due to cardiovascular causes was also considered. The protocol of both trials was similar. Follow-up of patients in both trials was 4 years.

In the CARDS trial statistically significant differences were observed in the primary endpoint in favour of the group treated with atorvastatin when compared to the placebo group (5.8% vs 9%). However, in the ASPEN trial no differences were observed when compared to placebo (13.7% versus 15.0%).

Precaution in use[1]

Liver affectation: Liver function tests are recommended before and after treatment and in those patients with suspected liver abnormalities**.** Treatment with A/A should be discontinued when AOT/GOT or APT/GPT levels reach three times the normal range. This agent should be employed with precaution in patients with important alcohol ingestion, liver damage, and/or history of liver disease.

Effects on skeletal muscle: This combined agent can produce myalgia, myositis, myopathy, rhabdomyolisis, mioglobinaemia, and myoglobinuria that can lead to renal impairment and could cause death in rare cases. Monitoring should be carried out before starting treatment with statins in patients with predisposing factors for rhabdomyolsis and in those patients that are already under treatment with statins who present with muscle derived symptoms

Contraindications

· Hypersensitivity to dihydropyridines, the main active substances amlodipin and atorvastatin or any of the excipients.
· Active liver disease or unjustified and persistent increments in liver transaminases that are three times higher than the upper limit of normal.
· During pregnancy and lactation.
· Combinations with itraconazole, ketoconazole and telitromycin

Interactions

The combination A/A with dantrolene (infusion), gemfibrozil, and other fibrates is not recommended. As with other drugs of the statín class, the risk of rhabdomyolisis and myopathy increases when A/A is administered concomitantly with certain agents that can increase the plasmatic concentrations of atorvastatin. These agents include: immunosuppresors, macrolides, azole antifungal agents, nefazodone, doses of niacin that modify lipids, gemfibrozil, other fibrates or HIV protease inhibitors.

Special situations

Renal impairment: no dose adjustments are required. **Children/adolescents:** no data on efficacy or safety has been established in children and adolescents. Therefore its use is not recommended in this population. **Elderly:** no dose adjustments are necessary in elderly patients.

Place in therapeutics

The efficacy of statins in reducing cardiovascular risk in patients with hypertension in primary prevention with normal cholesterol levels has not been demonstrated. Precisely, the addition of low dose atorvastatin in hypertension patients with three cardiovascular risk factors has shown only discreet results, with no reduction in mortality in populations with a high prevalence of coronary disease. Our population has a low risk, and therefore the expected efficacy would be even lower. The results of the amlodipin-atorvastatin combination in these patients are still unknown. Given that the use of these drugs will necessarily be associated with an increase in adverse effects and costs, the risk-benefit and cost relationships do not favour this practice.

On the other hand it should be taken into account that the association of both active substances at fixed doses in only one tablet makes it difficult to make any dose adjustments in patients treated for hypertension and dyslipidemia.

Presentations

Caduet® (Pfizer) and Astucor® (Almirall-Prodes Farma). Amlodipin 5 mg + atorvastatin 10 mg 28 tablets (26.44 €) and amlodipin 10 mg + atorvastatin 10 mg 28 tablets (34 €). Requires medical prescription.

References

The complete report on the combination amlodipin plus atorvastatin is available at: http://www.navarra.es/medicamento

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