European Review for Medical and Pharmacological Sciences 2012; 16: 1117-1119

Amlodipine in pediatric patient with uncontrolled multifactorial hypertension. Formulation of amlodipine oral suspension

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Abstract. – OBJECTIVE, To describe the case of treatment with amlodipine in a poorly controlled hypertension in a pediatric patient diagnosed with tricodistrofia.

CASE SUMMARY, Girl 5 years old, diagnosed of tricodistrofia included within the Tay-Sachs syndrome.

As a consequence of a cardiac arrest suffered in the context of a respiratory distress syndrome associated with infection by influenza A, she developed hypertension initially treated with nifedipine and captopril.

After several months of treatment and a poor control of the hypertension, a change of treatment was decided, substituting nifedipine by amlodipine (2.5 mg/24 hours orally) and captopril by enalapril (2.5 mg/24 hours orally). Pharmacy service is request to get a amlodipine syrup that allows a dose adjustment to the needs of the patient.

After the change of treatment the patient begins to maintain diastolic blood pressure levels within the normal range, suspending the administration of enalapril, maintaining good control of blood pressure with amlodipine 2 mg/24 hours.

DISCUSSION, Most of antihypertensive drugs used in adults do not have clinical trials to evaluate its effects in the pediatric population. Furthermore, the lack of familiarity with the pharmacokinetic characteristics of the child, raises problems to adjust the dose to the changing reality of a child. In this situation, clinical experience supports the use of some of these drugs in children with optimal results. With the addition to the pediatric field of calcium antagonists and ACE-inhibitors or ARB-II, they allow as to have greater potential therapeutic alternatives.

Key Words:
Amlodipine, Hypertension, Calcium antagonists.

Introduction

Amlodipine is a dihydropyridine with the capacity to antagonize the slow calcium channel voltage-gated L-type, showing a special affinity for the channels present in vascular smooth muscle. Amlodipine causes an intense arteriolar vasodilation by decreasing levels of intracytoplasmic calcium. Unlike other calcium blockers such as verapamil or diltiazem, dihydropyridines just have depressant effects on cardiac conduction, and in fact they often lead some reflex tachycardia.

As a result of vasodilation, it causes a reduction in peripheral resistance and blood pressure. Amlodipine, compared to other dihydropyridines, has a slower and prolonged effect. Reducing blood pressure can take 10 hours to become manifest, but the hypotensive effect is seen within 24 hours, with minimal risk of orthostatic hypotension.

Case Report

Girl 5 years old, diagnosed of trichodystrophy (skin and hair disorders secondary to defects in DNA repair) included within the Tay-Sachs Syndrome that presents with involvement of different organs and systems.

She has needed several hospitalizations by bronchitis with bronchospasm, atelectasis, bronchopneumonia and episodes of apnea. She presents osteosclerosis, global retinopathy signs and bilateral optic nerve injury. Carrier of nasojejunal tube feeding.

From a neurological point of view she presents a picture of psychomotor retardation caused by brain myelination disorder, left facial paralysis, horizontal nystagmus, spasticity, ataxia predominantly in lower limbs and cognitive delay.

Following a cardiac arrest suffered in the context of respiratory distress syndrome associated with an infection by influenza A, she developed a transient oliguria that required treatment with furosemide perfusion and hypertension (HTA) initially treated with nifedipine and captopril. A CT-angiogram is realized demonstrating the ab-

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sence of alteration in the renal artery and an echocardiogram study, which objectively mild pulmonary hypertension and left ventricular hypertrophy.

After several months of treatment and poor control of hypertension, we decided a change in therapy: furosemide is suspended and nifedipine is replaced by amlodipine (2.5 mg/24 hours orally) and captopril by enalapril (2.5 mg/24 hours orally). Unable to adapt available presentations from amlodipine to the needs of the patient, it was requested to Pharmacy Department a amlodipine syrup that allows the administration of the prescribed dose according to patient characteristics. After a literature search, it is set a method preparation of oral suspension Amlodipine 1 mg/ml, using as a vehicle a 1:1 mixture Ora-Plus and Ora-Sweet, with a stability of 56 days at room temperature and 91 in the refrigerator, being necessary in both cases the protection of light[1].

After the change of treatment the patient begins to maintain diastolic blood pressure (BP) levels within the normal range around 55-65 mmHg, occasionally persisting tendency to higher systolic blood pressures up to 120-140 mmHg, possibly related whit his neurological status.

At 6 months, echocardiography control is realized to assess the possible impact on the target organ. No abnormalities are detected on echocardiography and she has a tubular function within normal, so a reduce of the dose of enalapril is decided to withdrawal and a dose adjustment of amlodipine in 2 mg/24 hours. In subsequent checks good control of blood pressure were found.

Since the start of treatment there have not been observed adverse reactions related to treatment with amlodipine.

Discussion

Blood pressure is a parameter that increases progressively in relation to growth and body development over the years, a pattern that also differs by gender. The normal values published by the Task Force for Blood Pressure in Children[2] have been considerably modified by the chronological age, sex and percentile talla[3].

Hypertension is defined as blood pressure (BP) systolic and/or diastolic above 95 percentile specific for age, sex and height, in three or more occasions. The values of systolic and/or diastolic greater than or equal to 90 but below 95 are considered prehypertension.

In many cases the presence of hypertension in childhood is the result of a number of underlying pathologies, which the first manifestation can be the hypertension, is what is known as secondary hypertension. A small percentage of pediatric patients have hypertension monogenic, since it has been established Mendelian association, in which a mutated gene leads to hypertension in a high proportion of members of a familia[4]. In most part of the hypertension is not possible to identify any underlying cause so that essential hypertension is the most frequent. The growing identification of adolescents with essential hypertension leads to general acceptance that essential hypertension has its roots in pediatric age, so that a early of blood pressure control can reduce the prevalence of hypertension in adulthood with the consequent decrease in cardiovascular morbidity and mortality.

The treatment of hypertension in a child is very complex, although most cases are resolved with pharmacological treatment, in some cases a surgical approach is required. The therapeutic approach for hypertension should include not only drug use but also the non-pharmacological measures. Consideration of its use may be based on the values of BP, the presence of a defined etiology, and assessment of potential risk factors.

The objectives of the therapy are to normalize the BP, reverse target organ involvement, use a minimal drug dose and get good compliance treatment[5].

Antihypertensive drugs used in adults are also used in children, but in most cases there are no studies evaluating its effects in the pediatric population. Clinical trials that help to establish effective and safe guidelines in adults are rare in children. Furthermore, the lack of familiarity with the pharmacokinetic characteristics of the child, raises problems to adjust the dose to the changing reality of a child, a factor that binds to the technical difficulty of adapting sales presentations to a formulation that allows the administration in children.

At the start of antihypertensive treatment can be approached from a classical point of view by the staggered combination of diuretics, beta blockers, classic vasodilators and a centrally acting drug. With the addition to the pediatric field of calcium antagonists, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin re-

ceptor blockers II (ARB-II), the demonstration of its effectiveness and the lack of secondary effects, allow now more powerful therapeutic alternatives to the traditional model.

After the installation of a calcium antagonist in case of failure to achieve an adequate control of BP, the most suitable drug for combination is an ACE inhibitor. It allows us to use of lower doses of both partners, because they have distinct mechanisms of action, the simultaneous use generates an synergistic action[6].

In the case of this patient was chose the association of calcium antagonists plus ACE inhibitor, without getting a control of BP levels with the first association, nifedipine plus captopril. However, the combination of amlodipine plus enalapril, and after with the withdrawal of ACE inhibitors, amlodipine monotherapy allowed to control hypertension in this child. The result of this treatment seems to be defined by the pharmacokinetic characteristics of the calcium channel blocker.

Amlodipine and nifedipine are two calcium antagonists of the dihydropyridine group, effective in single daily administration and with few secondary effects[7-9]. However, due to the intrinsic properties of the amlodipine molecule, this has a slow absorption (6-12 hours after oral administration), a bioavailability of 64-80% due to the high hepatic first-pass effect and a long elimination half-life (36 hours after a single dose and 45 hours after repeated doses). These features allow a gradual decline in blood pressure with a single daily dose[10-13]. Furthermore, nifedipine has a more rapid absorption, reaching peak levels after 0.5-2 hours (in standard formulations) and has a half life of 2-5 hours, without ensuring the reduction in blood pressure for 24 horas[14].

In conclusion, the combination of enalapril and amlodipine, and later the amlodipine in monotherapy, has allowed to control of hypertension in this patient, avoiding the manifestation of secondary complications due to the poor control of blood pressure that would hinder the evolution of the underlying disease of the patient.

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