EDITORIAL

Angiotensin-converting enzyme inhibitors in the treatment of hypertension

ANA MARÍA DE DIOS[MTSAC], [1]

Prevention of vascular disease associated with hypertension is a global priority issue in health policies worldwide. (1)

The prevalence of high blood pressure (HBP) in childhood is 1-3%, and reaches 10% in adolescence, especially among obese patients.

During the early stages of life, 90% of the cases of HBP are due to secondary causes, being renal or renovascular causes the most common ones, (2) while primary or essential hypertension is more common in adults with a significant family history (obesity, hyperlipidemia), and it is diagnosed by excluding other conditions.

In adulthood, blood pressure goals are lower than 140/90 mm Hg for all hypertensive patients, and lower than 130/80 mm Hg for high risk patients, like those with diabetes, post-stroke, heart disease, and chronic renal disease (even lower for patients with significant proteinuria). (3)

The choice of medication will depend on the cause of HBP and the associated complications.

Blood pressure (BP) must be gradually lowered, and it is often necessary to combine two or more antihypertensive drugs. (4)

In the group of high-risk hypertensive patients, and in those with repeated BP > 160/100 mm Hg, the use of antihypertensive drug combinations from the beginning should be considered, so that further antihypertensive efficacy without high doses, fewer adverse effects, and synergy in target organ protection are achieved with these combinations. (5)

The pharmacological groups that proved effective in lowering blood pressure and in reducing morbidity and mortality are angiotensin-converting enzyme inhibitors (ACE), angiotensin II receptor blockers (ARBs), calcium antagonists, beta blockers, and diuretics. (6)

ACE inhibitors are commonly prescribed to women at childbearing age, without taking into account that, in general, pregnancies are not planned, and women with chronic diseases (hypertension, obesity, diabetes) and under previous medical treatment do not come to consultation when they get pregnant in order to discontinue or change the medication prescribed before their pregnancy.

In this population, several cases of major cardiac malformations (MCM) would be prevented if prescription and use of ACE inhibitors were avoided, since their teratogenic effect during the first trimester of pregnancy has been demonstrated. (7)

Fetuses exposed to the inhibitory effect of these drugs during the first trimester of pregnancy have an increased risk of 2.71 for MCM compared with those not exposed to antihypertensive drugs in the same trimester. According to recent observations, fetus exposure to ACE inhibitors during the first trimester of pregnancy increases the risk of MCM, half of them due to ventricular septal defects, and the other half due to CNS malformations, or defects in the urologic system or in other systems.

The use of ACE inhibitors during the second and third trimesters is contraindicated because their in-uterus effect is associated with fetopathies, since it affects fetal kidney development and fetal intrauterine growth, causes oligohydramnios, fetal renal dysplasia, anuria and kidney failure, and even fetal death.

If ACE inhibitors are teratogenic during early pregnancy by their expression on angiotensin II receptor blockers, one might assume that ARBs II may also be teratogenic.

However, the mechanism by which the various reported congenital malformations occur is still unclear.

Angiotensin-converting enzyme inhibitors include: benazepril (Lotensin), captopril (Capoten), enalapril/enalaprilat (Vasotec, oral and injection), fosinopril (Monopril), lisinopril (Zestril and Prinivil), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace), and trandolapril (Mavik).

So far, the risk of fetophaties was known to exist over the last six months of pregnancy, particularly those related with kidneys and similar structures; the findings reported by the study of Bernztein and Drake –published in this issue of the Revista– (8) made it possible to confirm the importance of avoiding their use throughout pregnancy.

ACE inhibitors are labeled with a pregnancy category D for women during the last six months (the second and third trimesters) of pregnancy, and category C for the first three months.

Pregnancy category D means that there have been studies in pregnant women showing that the drug was

[MTSAC] Full Member of Sociedad Argentina de Cardiología
[1] Chief of Cardiology Unit - Hospital de Niños Pedro de Elizalde
Director of the Council of Pediatric Cardiology and Congenital Heart Diseases in the Adult, of Sociedad Argentina de Cardiología

associated with some risk for the unborn baby, but the benefit of the drug may still outweigh that risk for some patients.

Pregnancy category C means that the risk in pregnancy is possible but unknown, because no good studies of pregnant women have been done, and there are no studies of animals either.

If we take into account that ACE inhibitors are potentially teratogenic, its use in women of childbearing age should be limited. (8)

The study by Bernztein and Drake focuses on the same idea; it states that prescription of enalapril (an ACE inhibitor) to women of childbearing age covered by the Remediar Program should be carefully evaluated considering the risk of MCM in the fetus, accidentally exposed to ACE inhibitors during the first trimester of pregnancy since it is a potential generator of serious disease; avoiding it would have a strong impact on primary prevention of major congenital malformations.

The FDA recommends that:

- Health agents inform women of childbearing age about the potential risk of ACE inhibitors during pregnancy, especially in the second and third trimesters.
- Pregnant women be prescribed ACE inhibitors only if the benefit of the drug outweighs the potential risk of use.
- Women who become pregnant should be changed medication as soon as possible.
- Women taking ACE inhibitors due to high blood pressure should inform their treating physicians about their plans to become pregnant, in order to define the treatment strategy.

Unfortunately, pregnancies are not always planned, not even reported to treating physicians.

In January 2010, the United States Department of Health and Human Services (HHS) announced the categorization and national registry of fetal injury related to drugs. (9) The parameters taken into account were the time of exposure (first trimester or

Exposition in the first trimester	Born	BD	BD/1.000 LBs	OR (95%) on all the LBs
All the LBs in 2002-2005	106,074	4,995	47	
LBs exposed to 47 medications	1,968	139	71	1.68 (1.3-1.9)
Medroxyprogesterone acetate	820	67	82	1.8 (1.4-2.3)
Paroxetine hydrochloride	603	25	41	0.9 (0.6-1.3)
Valproate sodium	97	6	62	1.3 (0.6-3.1)
Carbamazepine	97	13	134	3,1 (1,7-5,6)
Follitropin alpha	82	9	110	2.5 (1.2-5.0)
Lamotrigine	45	< 5	67	1.4 (0.4-4.7)
Atorvastatin calcium	33	< 5	30	0.6 (0.1-4.6)
Perindopril erbumine	32	< 5	94	2.1 (0.6-6.9)
Azathioprine	29	< 5	69	1.5 (0.4-6.3)
Hydroxychloroquine sulphate	26	< 5	115	2.6 (0.8-8.8)
Ramipril	22	< 5	136	3.2 (0.9-10.8)
Irbesartan	21	< 5	143	3.4 (1.0-11.5)
Simvastatin	18	< 5	56	1.2 (0.2-8.9)
Phenytoin sodium	14	0		
Norethisterone	10	< 5	100	2.2 (0.3-17.8)
Perindropril erbumine, with indapamide hemihydrate	9	< 5	111	2.5 (0.3-20.2)
Irbesartan with hydrochlorothiazide	8	< 5	125	2.9 (0.4-23.5)
	7	< 5	143	3.4 (0.4-28.0)
Interferon Beta-1B	7	< 5	286	8.1 (1.6-41.7)
Enalapril maleate	6	< 5	167	4.0 (0.5-34.7)
Quinapril hydrochloride	< 5	< 5	250	6.7 (0.7-64.9)
Isotretinoin	< 5	< 5	333	10.1 (0.9-111.6)
Ethosuximide	< 5	< 5	500	20.2 (1.3-323.6)
Quinapril hydrochloride, with hydrochlorothiazide				

Category D: Drugs which have caused, are suspected to have caused, or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. **Category X:** Drugs which have a high risk of causing permanent damage to the fetus and should not be used in pregnancy or when there is a possibility of pregnancy. **LB**: Live birth. **BD**: Birth defect.

Table 1. Defects in the newborn that received medications included in categories D or X during the first trimester of pregnancy in the 2002-2005 period by the number of pregnancies exposed.

later), and the likelihood of fetal injury per 1,000 live births (Table 1).

The defects identified in this study included bulbus cordis and septal closure anomalies and other heart defects, abnormalities in the circulatory system and the genitals.

Interatrial defect, pulmonary stenosis, and atrioventricular septal defects had been previously reported, (10-12), as well as CNS malformations and prolonged renal failure in neonates, and renal tubular dysgenesis with reduced skeletal ossification.

Alterations reported in the second and third trimesters included hypotension, renal failure, fetal hyperkalemia, disorders in the renal function in the fetus and the neonate, neonatal anuria with skeletal hypoplasia, and death.

There is a strong presumption that renal dysfunction is more common with the use of enalapril than with captopril; therefore, it is recommended to limit their use, and in case they are prescribed, to warn women of childbearing potential so that they can adopt safe contraceptive measures.

BIBLIOGRAPHY

1. Macmahon S, Alderman MH, Lindholm LH, Liu L, Sanchez RA, Seedat YK. Blood pressure-related disease is a global health priority. Lancet 2008; 371:1480-2.

2. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 114:555-76.

3. Grupo de Hipertensión. Consenso sobre factores de riesgo de enfermedad cardiovascular en pediatría. Hipertensión arterial en el niño y el adolescente. Arch Argent Pediatr 2005; 103:348-66.

4. Bendersky M. Asociaciones de drogas en hipertensión arterial. Rev Fed Arg Cardiol 2010; 39:16-21.

5. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. CMAJ 1999; 160:41-6.

6. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the content of expectations from prospective epidemiological studies. BMJ 2009; 338:b1665.

7. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006; 354(23):2443-51.

8. Bernztein RG, Drake I. Prescripción de enalapril a la mujer fértil como factor de riesgo de malformaciones congénitas en el primer nivel de atención pública de la Argentina. Rev Argent Cardiol 2011; 79:XXX-XXX.

9. Colvin L, Slack-Smith L, Stanley F, Bower C. Linking a pharmaceutical claims database with a birth defects registry to investigate birth defect rates of suspected teratogens. Pharmacoepidemiol Drug Saf 2010; 19:1137-50.

10. Buhimschi CS, Weiner CP. Medications in pregnancy and lactation: part 1. Teratology. Obstet Gynecol 2009; 113:166-88.

11. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998;338:1128-37.

12. MIMS Australia Pty Ltd. Monthly Index of Medical Specialties Online. 2009 [cited 11 June 2009]