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Successful pregnancy in a severe hypertensive patient treated with nitrendipine. Case report.

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Abstract. Nitrendipine (NIT), a new potent calcium channel blocking agent, was administered to a patient with essential severe (191/119 mm Hg), refractory, and resistant hypertension (HT) to conventional triple drug regime. Three previous pregnancies had been unsuccessful in the past 4 years because of uncontrollable HT and repeated hypertensive crisisses. NIT (20 mg tablets) was given PO as a single morning dose and 15 months after BP control, she became pregnant again. With a 20 mg/day dose of NIT throughout pregnancy, a healthy 2400 g, 47 cm male boy was delivered by a non-emergency cesarean section at 37 weeks' pregnancy. Both mother and son remain normal months after birth. The results suggest NIT may be considered as an alternative for this type of patients and should be studied in clinical trials.

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INTRODUCTION

Severe hypertension (HT) associated with pregnancy is a difficult situation with specific problems. When blood pressure (BP) is too high, difficult to control, or presenting repeated hypertensive crisisses, the accepted treatment is to deliver the fetus. However, recent reports are available on the treatment of this situation with variable results (4). Advances in antihypertensive therapy have made pregnancy safer in severe hypertensive high-risk patients; angiotensin I converting enzyme inhibitors (ACEI) and calcium-channel blocking agents (CCBA) are potent, effective and useful antihypertensive

drugs currently available in the treatment of severe HT and HT with associated diseases or with pregnancy (1, 2, 4, 7, 10, 15, 17, 20).

We report a case of a woman with severe resistant HT difficult to control, with 3 previous pregnancy losses due to HT and hypertensive crississes, who after satisfactory control of her high BP with nitrendipine (NIT), a novel dihydropiridine derivative with calcium-channel blocking and vasodilating properties, had an uneventful gestation and delivered a normal child by cesarean section, in order to contribute to the benefit of this type of high risk pregnancies.

MATERIALS AND METHODS

Case report.

N. de P., a 34-year old Executive Secretary gravida 3, was a known severe hypertensive patient that was referred to the University Hospital's Hypertension Clinic because of severe, resistant, and refractory essential HT difficult to control (8) and with repeated hypertensive crisisses (1 to 3 per month). Her BP values were variable between 180/155 to 220/130 mm Hg (191.5 ± 4.43/119.5 ± 3.6 mm Hg, M ± SEM, n = 6, fig. 1). She was being treated with a triple drug regime consisting of propranolol, hydralazine and furosemide; previously she had received thiazide diuretics and ACEI (captopril and enalapril) all in adequate dosage and compliance but having either intolerance or uneffectiveness. She had a history of 3 lost pregancies in the past 4 years: two 18th and 19th weeks fetal losses and a 32-week neonatal dead girl, all related to high BP values and hypertensive crisisses with severe emotional distress for both parents; during these pregnancies she received both antihypertensive, dietetic and strong psychological and psychiatric care as it was during the present pregnancy. Placental ischaemia was demonstrated in all 3 cases, consisting on vascular sclerosis, lipomatosis and thickening, placental low weight and infarct areas both whitish and hemorrhagic. She had severe HT with grade II retinal fundoscopy and deeply depressed but was otherwise in apparent good health with normal renal function and ECG. Psychiatric help was obtained throughout the follow-up period and thereafter, in the same way as it was during the previous 3 lost pregnancies. Secondary forms of HT and any other systemic disease were ruled out. A full gynaecologic and ultrasonographic evaluation showed no breast tumors, a normal Pap smear and a nodular uterine's anterior wall leiomyomata that was asymptomatic.

Because of the severity of her HT, her low plasma renin activity of 0.4 ng/ml/h (11) (normal values in our laboratory = 0.27-2.7 (14)), the apparent lack of success of ACEI and other antihypertensive drugs in controlling her high BP (10,18), and the reported efficacy of CCBA (especially NIT) in mild to moderate and severe HT (1, 2, 3, 5, 7, 10, 12, 20), NIT was chosen for her treatment and administered as a single morning 40 mg/day oral dose; her BP could then be controlled and maintained at varying levels between 150/80 and 130/75 mm Hg (Fig. 1) presenting

light tolerable throbbing headache and facial redness.

BP at an average of 120/70 mm Hg throughout pregnancy and immedi-

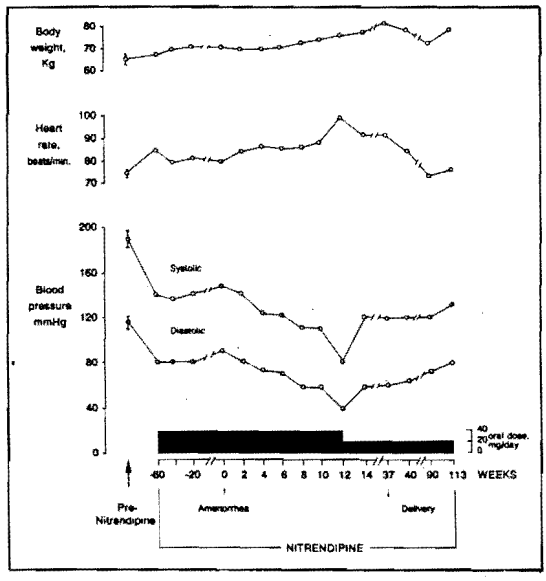

Fig. 1. Hemodynamic course and nitrendipine effect on the patient.

Pregnancy and outcome.

Fifteen months after satisfactory hemodynamic control and highly anxious to have her own child - since she strongly refused adoption- she became pregnant for the fourth time (Fig. 1). After approval from the ethics committee of our Hospital and both patient and husband's written consent, NIT was continued at the same dosage maintaining BP values at an average of 120/70 mm Hg and heart rate of 84 per min, presenting mild ankle edema at week 10th of gestation. At week 12th of gestation this dose had to be reduced to 20 mg/day because of mild symptoms of hypotension and low BP values (80/45 mm Hg, Fig. 1). This new dose was sufficient to keep her ate post-partum period without noticeable side effects (Fig. 1). Renal function was unchanged and fetal distress was not observed.

During pregnancy BP (measured all the time with an automatic cutoff), body temperature and weight were measured daily. Renal and liver functions and ECG as well as general being were checked every 2 weeks, and every week in the last trimester. Routine obstetric and psychiatric care took place every week from the beginning and additional check-ups were made if necessary. Ultrasonographic controls and cardiotachography were performed at each obstetric examination after the 10th week of pregnancy showing no fetal distress and confirming the uterine myoma. The fetal heart rate records

were normal as were the Doppler velocity waveforms of the umbilical arteries. All patients'tests remained normal as well as fetal growth and amniotic fluid.

She was admited to the Hospital at week 12th of gestation because of mild vomiting and enhanced anxiety, and was discharged 3 weeks later after appropiate support and treatment. There were no changes in either mother's or fetus' evolution and she was in good and stable conditions. Because uric acid was raising, the patient had increasing anxiety with emotional distress, and the presence of an uterine leiomyomata, a non-emergency elective lower-segment cesarean section was performed at 37 weeks' gestation under peridural anaesthesia 4 hours after that day's NIT dose; an apparently healthy 2400 g, 47 cm male infant was delivered without complications on July 29th, 1988. The baby had an Apgar score of 8 and 9 at 1 and 5 min respectively, did not require respiratory support, voided urine spontaneously, and the examination showed no evidence of congenital anomalies, a normal biochemical and hematological profile, including arterial pH and acid-base parameters, and had an uncomplicated course in the nursery. The placenta weighed 300 g and was grossly and histologically normal. Amniotic fluid was thought to be less than normal but was not measured. Mother and son remain in good health 48 months after delivery. The patient's BP values remain stable at 130/80 mm Hg with a 20 mg/day single oral dose of NIT (Fig. 1) and the child, under pediatric care, has had a normal physical, emotional and intelectual development to date, as judged from his clinical, hematological and biochemical evaluations, his normal growth rate and physical-psychological evaluations, the absence of any pathological situation and the fact that he is in kinder-garten school performing as any other child in class.

The child was breast-fed for 6 months after birth. It was observed on several ocassions that 90 to 120 min after breast- feeding he had mild facial redness and warmth, which are attributed to calcium antagonists' vasodilatory effect.

DISCUSSION

Outside pregnancy, severe HT difficult to control is a serious situation, and within pregnancy it places additional burden (4, 15, 20) so that the association of severe HT and pregnancy is a subject of continued concern since it produces both maternal morbidity-mortality and high perinatal mortality. Although major emphasis is placed on the benefit of the fetus, maternal physical and emotional needs may be equally important, as illustrated in our case where additional concern was produced by the emotional weight imposed on both parents: she was in her mid-thirties and had had 3 previous pregnancy losses so far.

Although references are scarce, the availability of potent and safe vasodilator drugs suggests that the severe and/or refractory HT may be controlled (2, 3, 7, 10, 18), the favorable evolution and successful outcome of a pregnancy associated with severe HT seems possible nowadays.

Thus, it may be highly advisable for the patient to obtain a safe and stable BP control in order to become pregnant again as illustrated in this case (Fig. 1). After that, the severe hypertensive pregnant woman should be supported to provide continued and vigorous BP, somatic and emotional normal functioning and control and therefore, the potential for development and growth of her fetus.

The drug choice for treatment schould be one of potent vasodilator properties (1, 4, 7, 10, 15, 16, 20) that ensures a successful pregnancy and the output of a normal child. It envolves both the hemodynamic stability of the mother and the utero-placental circulation. The utero-placental vasculature is normally responsive to α-adrenergic estimulation (9), and on the other hand, in newborns, arterial pressure is low and renal autoregulation might be warranted by the highly activated renin-angiotensin system (13). The severe increase in systemic vascular resistance associated with the HT is consistent with the anticipated vasoconstriction that might decrease utero-placental blood flow and jeopardize the fetus; thus, it seems more reasonable and convenient to cause a direct decrease in systemic vascular resistance than an indirect one and maintain the renin- angiotensin system activated. In such conditions, ACEI do not seem adequate enough and additionally, neonatal anuria has been described after administration of captopril (16) and enalapril (17) during pregnancy. On the contrary, CCBA may provide several advantages in this type of situation. They are among the most useful antihypertensive drugs for the treatment of HT with associated diseases and difficul to control (1, 2, 3, 7, 10, 18); both verapamil (15) and nifedipine (20) have appeared safe and effective in the control of BP values in patients with HT associated with pregnancy (4). CCBA may activate the renin- angiotensin system (2, 3, 12) and interfere with the reflex increase in sympathetic activity and α -adrenergic-mediated vasoconstriction (6) in the umbilical arteries (9) by their α-adrenergic inhibitory action (19). Also, the magnitude of BP reduction appears to be directly related to pretreatment BP values and inversely related to pretreatment renin values (2, 11), which this patient had. Moreover, there is no reported evidence of mutagenesis, carcinogenesis, or teratogenicity associated with the use of either NIT or CCBA so far and NIT is pharmacologically a more convenient drug than the preexisting CCBA available (1, 2, 5, 7, 10, 12, 18).

For all the aforementioned data, the characteristics of NIT, the fact that this particular patient had been on a previous multidrug antihypertensive regime (3, 18) including ACEI, that failed to control her high BP, and the potential benefits on a possible future fetus (12, 16, 17, 20), we decided to treat her with NIT and to continue with it once pregnancy occurred. In this case, NIT was able to reduce BP satisfactorily in a patient with HT difficult to control (2, 3, 7, 8, 10, 18) and under its effects, pregnancy was straightforward with no threatening events apart from her constant aprehension of losing her probable last chance of having her

own child, according to her own conviction. Delivery was prompted mainly by her emotional instability and the increasing levels of uric acid.

The issue of costs was also important within the context of the requirements for extra care and managements. Nevertheless, both the parents and medical staff consider is justifiable and highly rewarding in view of the final outcome. Too few cases -if any - have been previously reported in this situation to evaluate the rate at which NIT or CCBA may help to provide sustained non-complicated pregnancies with healthy newborns in patients with severe HT difficult to control, but from this single case it would seem that whith adecuate evaluation, care and hemodynamic control, as illustrated by the evolution and outcome of this pregnancy, both hemodynamic status and pregnancy may progress uneventfully where multidrug antihypertensive regime is neither efficient nor tolerable, provided it is previously hypertensive patient who becomes pregnant with low renin values.

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RESUMEN

Embarazo exitoso en una paciente hipertensa severa tratada con nitrendipina. Reporte de un caso. Colina-Chourio J. (Cátedra de Fisiología, Facultad de Medicina, Universidad del Zulia, Apartado 15182, Maracaibo, Zulia 4003-A, Venezuela), Godoy N., Oliveros- Palacios M., Nery-Villarroel M., Arocha I. *Invest Clin 33(2): 61 - 67, 1992.*

Nitrendipina (NIT), un nuevo calcio-antagonista potente, se administró a una paciente con hipertensión arterial severa (191/119 mm Hg), refractaria y resistente al tratamiento de triple cura convencional. En los últimos 4 años había tenido 3 pérdidas gestacionales debidas a hipertensión incontrolable y crisis hipertensivas repetidas. Se administró NIT en tabletas de 20 mg vía oral en dosis única matutina, y después de 15 meses de buen control de presión arterial tuvo un nuevo embarazo. Con dosis de 20 mg/día de NIT durante el embarazo, se obtuvo un niño de 2440 g de peso y 37 cms de estatura a las 37 semanas, a través de cesárea selectiva. Tanto la madre, como el niño permanecen normal meses después del nacimiento de éste último. Los resultados sugieren que NIT puede ser considerada como una alternativa en éste tipo de pacientes y debe estudiarse en ensayos clínicos.

REFERENCES

1- AMBROSIONI E., BORGHI C.: Calcium channel antagonistsin hypertension. Am J Hypertens 2:90s-93s, 1989.

2- COLINA-CHOURIO J.A., GODOY N., OLIVEROS-PALACIOS M., AROCHA I.: Long-term (3 years) sustained antihypertensive and metabolic actions of nitrendipine in

severe, complicated, and resistant hypertension. J Cardiovasc Pharmacol 18(Suppl. 1):s84-s90, 1991.

3- COLINA-CHOURIO J., OLIVEROS-PALACIOS M.Ch., GODOY N.: Nitrendipine: a slow calcium channel blocking agent that reduces high blood pressure and promotes renal hormones and function changes in severe hypertension. J Hypertens 6(Suppl):64, 1988.

4- DeSWIET M.: Antihypertensive drugs in pregnancy. Br Med J 291:365-366, 1985.

5- ESPER R.J., ESPER R.C., BAGLIVO H., CASTRO J.M., ROHWEDDER R.W., MENNA J.: Long-term effectiveness of BAY e 5009- Nitrendipine in the treatment of mild to moderate arterial hypertension. J Cardiovasc Pharmacol 6:s1096-s1099, 1984.

6- FLECKENSTEIN A., FREY M., ZORN J., FLECKENSTEIN-GRUN G.: Experimental basis of the long-term therapy of arterial hypertension with calcium antagonists. Am J Cardiol 56:3H- 14H, 1985.

7- FRISHMAN W.H., WEINBERG P., PEDEL H.B., KIMMEL B., CHARLAP S., BEER N.: Calcium entry blockers for the treatment of severe hypertension and hypertensive crisis. Am J Med 77 (2B):35-45, 1984.

8- GIFFORD R.W., TARAZI R.C.: Resistant hypertension: diagnosis and management. Ann Int Med 88:661-665, 1978.

9- GREISS F.C.: Concepts of uterine blood flow. Obstet Gynecol Annu 2:55-83, 1973.

10- HOFFLER R., STOEPEL K.: Nitrendipine in hypertension that is difficult to control. J Cardiovasc Pharmacol 6:s1060-s1062., 1984.

11- KIOWSKI W., BUHLER F.R., FADAYOMI M.O.: Age, race, blood pressure and renin: Predictors for antihypertensive treatment with calcium antagonists. Am J Cardiol 56:81H-85H, 1985.

12- LOUTZENHEIZER R.D., EPSTEIN M.: Calcium antagonists and the kidney. Am J Hypertens 2:154s-161s, 1989.

13- NUSSBERGER J., BUCHER H., SCHMID J.: The control of plasma aldosterone in mother and newborn in labour and in the post- natal period. Research on steroids. p. 547-557. North Holland Publishing Co. Amsterdam (Holanda). 1977.

14- OLIVEROS-PALACIOS M.Ch., GODOY-GODOY N., COLINA-CHOURIO J.A.: Effects of doxazosin on blood pressure, renin-angiotensin- aldosterone and urinary kallikrein. Am J Cardiol 67:157-161, 1991.

15- ORLANDI C., MARLETTINI M.G., CASSANI A.: Treatment of hypertension during pregnancy with the calcium antagonist verapamil. Curr Ther Res 39:884-893, 1986.

16- ROTHBERG A.D., LORENZ R.: Can captopril cause fetal and neonatal renal failure?. Pediat Pharmacol 4:189-192, 1984.

17- SCHUBIGER G., FLURY G., MUSSBERGER J.: Enalapril for pregnancy-induced hypertension: acute renal failure in a neonate. Ann Int Med 108:215-216, 1988.

18- SWALES J.D., HEAGERTY A., RUSSELL G.I., BING R.S., POHL J.E.S., THRUSTON H.: Treatment of refractory hypertension. Lancet i: 894-896, 1982.

19- van ZWIETEN P.A., van MEEL J.C.A., TIMMERMANS P.B.M.W.M.: Pharmacology of calcium entry blockers: Interaction with vascular alpha-adrenoceptors. Hypertension 5 (Suppl 2):8-17, 1983.

20- WALTERS B.N.J., REDMAN L.W.G.: Treatment of severe pregnancy associated hypertensoin with the calcium antagonist nifedipine. Br J Obstet Gynaecol 91:330-336, 1984.