Nifedipine reduces pressor responsiveness to angiotensin II in pregnant women

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Summary: OBJECTIVE. We assessed the action of nifedipine on vascular reactivity to angiotensin II (AII) in pregnant women at risk for hypertension.

METHODS. We studied eleven pregnant women (28-32 weeks' gestation) who had shown a 20 mmHg increase in basal diastolic blood pressure at AII infusion rates < 10 ng/kg/min (Effective pressor dose, EPD), and were therefore considered at high risk for the subsequent development of pregnancy-induced hypertension, according to Gant. After the AII infusion was completed, we allowed the patients 4 hours of rest to avoid interactions with the first test, then administered 10 mg nifedipine, and after 30 minutes repeated the test.

RESULTS. In all the 11 women the EPD after nifedipine administration had significantly reverted to normal (paired t-test: $p < 0.03$).

CONCLUSIONS. The efficacy of nifedipine in reducing the pressor response to AII suggests the involvement of intracellular free calcium in the vascular response to pressor agents in pregnancy, and supports the use of this drug in the treatment of pregnancy-induced hypertension.

Key words: Angiotensin; Pregnancy; Hypertension; Nifedipine.

INTRODUCTION

Pregnancy induced hypertension is characterized by a greater vascular reactivity than normotensive pregnancy ([1]). The maintained vascular response is similar to non-pregnant status, and is considered the most important pathogenetic determinant of the elevated blood pressure in pregnancy-induced hypertension (PIH). The intracellular free calcium seems to be in the background of such vascular reactivity in PIH ([2]) and is increased in pregnancy complicated by hypertension ([3]). We therefore designed a study aiming to modulate the vascular sensibility with the administration of nifedipine, a calcium channel blocker.

Twenty years ago, Gant introduced a test to assess the vascular reactivity in pregnancy, by infusing angiotensin II. He defined "effective pressor dose of angiotensin II" (EPD-AII) as the angiotensin infusion rate at which a 20 mmHg increase from the baseline diastolic pressure occurred, and demonstrated that women destined to develop PIH responded to lower doses of angiotensin than did women who remained normo-

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tensive throughout pregnancy. This feature largely preceded the clinical manifestation of hypertension. Therefore, an EPD-AII $\leq$ 10 ng/kg/min was considered highly predictive of subsequent PIH ([4, 5]). As the free intracellular calcium is hypothesized to be the ultimate mediator of angiotensin II action on arterial vessels, we decided to investigate the effect of nifedipine on the vascular sensitivity as evidence by the test of Gant.

A reduced vascular reactivity would demonstrate that intracellular free calcium is involved in the genesis of the vascular response.

PATIENTS AND METHODS

Eleven primigravidae, mean age 28 years (range 25-41) at risk for hypertension on the finding of increased resistance index at Doppler velocimetry of both uterine arteries at 20 weeks' gestation ([6]) were subjected to the AII-test between 28 and 32 weeks. None of our patients had hypertension, had been or were receiving aspirin prophylaxis or were receiving other medications, nor were on a special diet, at the time of testing.

We followed the infusion protocol previously experienced with magnesium pyrrolidine carboxylate and recently published ([7]). Before starting the test, the baseline diastolic blood pressure was assessed with an automated sphygmomanometer with the patient resting in a left lateral position. A solution of 1 μg/ml of angiotensin II (Hypertensin, Ciba-Geigy AG, Basel, Switzerland) in 0.9% sodium chloride was then infused by means of an automatic volumetric pump at variable pressure (IVAC 500, IVAC Corp. San Diego, CA, USA). The infusion was started at 2 ng angiotensin II/kg body weight per minute and increased by 2 ng/kg/min every 5 minutes, until a 20 mmHg increase from baseline diastolic blood pressure was achieved or an infusion rate of 32 ng/kg/min was reacherd. When the effective pressor dose was obtained, we stopped the infusion. After the diastolic blood pressure had returned to baseline, we confirmed the effective pressor dose restarting the infusion at the dose reached and observing the same diastolic blood pressure increase.

After the infusion of angiotensin was completed we allowed the patients 4 hours to recover from the first test and to avoid interactions with it. Then we administered 10 mg nifedipine (Adalat, Bayer Leverkusen, Germany) and after 30 minutes (necessary to reach maximum effect) we repeated the test according to the scheme described above.

The results were expressed as the mean and standard deviations of the EPDs-AII before and after nifedipine administration, and tested for statistical significance with the paired t test. Statistical significance was assessed for $p < 0.05$.

RESULTS

After nifedipine administration, the EPD was significantly increased and reverted to normal in all the cases, as illustrated in Fig. 1 (basal EPD 8.6 $\pm$ 0.9; post-nifedipine 16.1 $\pm$ 1.2, $p < 0.03$). Moreover, after nifedipine, none of the women could be considered as "sensitive/at high risk" any longer because the EPD-AII increased over the cut-off of 10 ng/kg/min ([4, 5]) in all the cases.

Notably, all these women, classified as "sensitive", evolved to a pathologic pregnancy: eight of them developed PIH, consistently with the clinical experiences of Gant ([4, 5]), while the remaining three women showed intrauterine fetal growth retardation, which could be considered a precocious clinical stage of hypertension, according to the recent observations of Nova and Sibai ([8]).

COMMENT

A significant modification of the vascular response to angiotensin II induced by the administration of a calcium channel blocker such as nifedipine, is demonstrated from the analysis of our results.

This suggests that intracellular free calcium is the ultimate messenger of the post-receptor compartment and constitutes the background of the increased pressor reactivity in pregnancy-induced hypertension.

This experience recalls what we had previously observed with the use of magnesium pyrrolidone carboxylate ([7]) and confirms the hypothesis that vascular re-

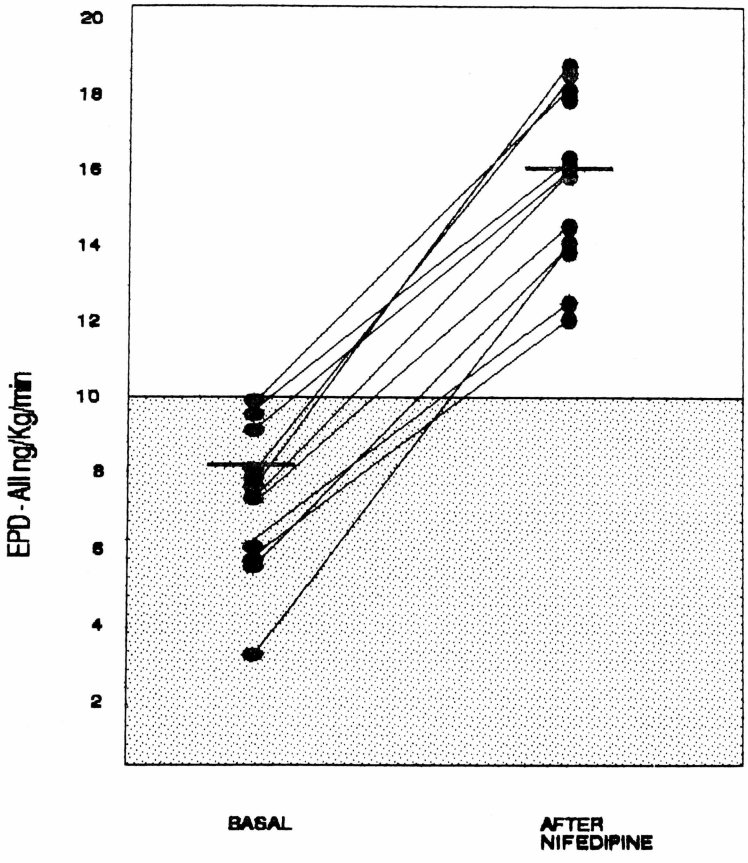

Fig. 1. — Modulation of pressor response to infused angiotensin II by nifedipine. The effective pressor dose (i.e. the amount of infused angiotensin II necessary to raise diastolic blood pressure 20 mmHg) is significantly increased after nifedipine administration. The horizontal bars indicate the mean ± SD (8.6 ± 0.9 vs. 16.1 ± 1.2, $p < 0.03$ Basal vs. post-nifedipine EPDs, $p < 0.03$). EPD expressed as ng infused angiotensin II / kg weight / minute.

sponse to vasoactive agents, angiotensin first, is mediated by intracellular calcium and nucleotides ([9]) rather than by central mediators, such as dopamine or catecholamines ([10]).

Since calcium channel blockers exert their effect on activated intracellular free calcium, we may hypothesize that the significant modification of vascular reactivity after nifedipine administration demonstrates the impairment of intracellular calcium metabolism in women destined to a subsequent pregnancy-induced hypertension.

The greater intracellular calcium availability is involved in the abnormal reactivity of the smooth muscle fibers.

The elevation of the EPD-AII after nifedipine confirms what Gant and coworkers found with dietary and pharmacologic ([11]) manipulations of the classic angiotensin test.

In conclusion, our results not only confirm the pathogenetic mechanism, which

is the background of PIH, but also suggests the rational use of this pharmacological class in the treatment of PIH.

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