"CALCIUM CHANNEL BLOCKERS IN TREATMENT OF PREGNANCY ASSOCIATED HYPERTENSION"

Thesis

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BY

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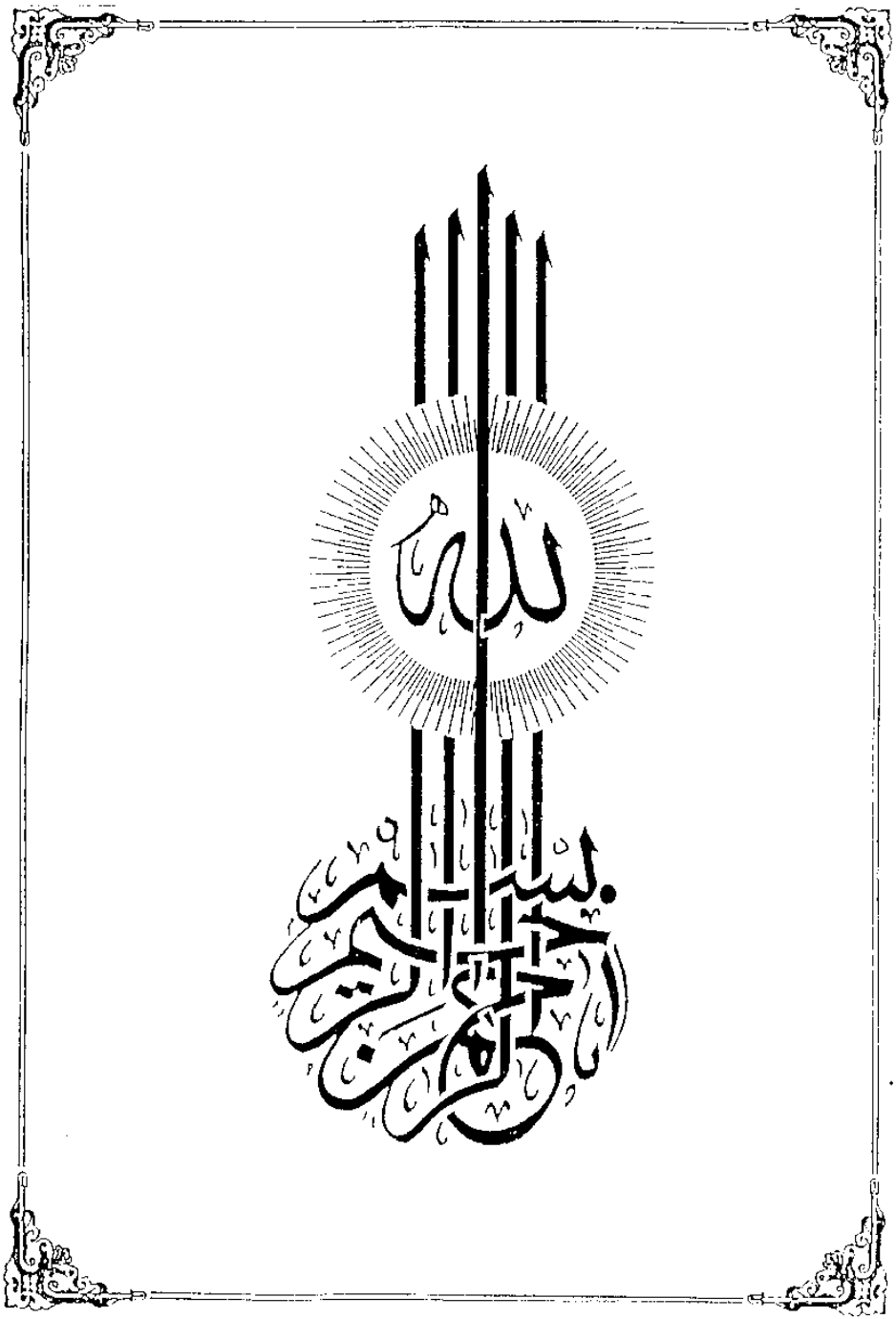
TABLE OF CONTENTS



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INTRODUCTION

Preeclampsia is still an unresolved common problem of pregnancy. The use of antihypertensive drugs in pregnancies complicated by hypertension is still controversial. Calcium channel blockers have a special appeal, as antihypertensives, as they act on the common pathway of hypertension which is calcium.

AIM OF THE WORK

- Assess the efficacy of Nifedipine in the management of preeclampsia.
- Assess the safety of Nifedipine to the mother and the fetus.
- Assess the benefits and the cost-effectiveness of prolonging pregnancy by using Nifedipine as an antihypertensive.

REVIEW OF LITERATURE

CALCIUM, PREGNANCY AND PREGNANCY-RELATED HYPERTENSION

Calcium Metabolism in Pregnancy and the Perinatal Period:

The mechanism of calcium homeostasis in pregnancy is multifactorial, involving calcium itself, other related minerals such as magnesium and phosphorus, and three calcitropic hormones: parathyroid hormone, calcitonin, and the active form of Vitamin D, 1,25-dihydroxyvitamin D.

The principal maternal adjustment during pregnancy is an increasing parathyroid hormone secretion which maintains the serum calcium concentration in the face of a falling albumin level, an expanding extracellular fluid volume, an increasing renal excretion, and placental calcium transfer. Thus, the intestinal absorption of the mineral is enhanced and the rate of bone turnover increases progressively.

Urinary calcium excretion has been reported in different studies both to increase and to decrease during late gestation but most authors agree that it increases and that the gestational increase in glomerular filtration rate is responsible. The total calcium concentration in maternal serum characteristically declines during gestation, reaching a Nadir during the middle third trimester and rising slightly thereafter. (Pitkin et al, 1977). The decline averages about 0.25 mEq/L or 5% to 6% from the preconceptional level, and the pattern parallels that of serum albumin, suggesting strongly that the fall involves the protein-bound fraction. Magnesium and phosphorus levels also tend to decline during gestation.

The pattern and extent of the gestational increase in parathyroid secretion are less clear. Some studies have suggested that the rise is limited largely to the third trimester and amounts to a doubling of the non-pregnant value whereas others have described a more gradual and progressive increase amounting to 30% to 50% by term (Reily et al, 1977 and Pitkin et al, 1979).

In theory, some increase in calcitonin secretion during pregnancy would seem reasonable physiologically in protecting the maternal skeleton from excessive parathyroid hormone-induced resorption while permitting the latter hormone's gut and kidney effects to continue.

The net effect is that of protecting the maternal skeleton from excessive resorption at times of hypocalcemia and promoting skeletal calcium storage when hypocalcemia occurs. The principal physiologic mechanism promoting renal hydroxylation of 25-hydroxyvitamin D3 is parathyroid hormone and it is tempting to point to "physiologic hyperparathyroidism" as the cause of increased 1,25-dihydroxyvitamin D3 formation in the pregnant woman. Other hormones known to promote 1,25-dihydroxyvitamin D3 synthesis which could be responsible are prolactin, growth hormone and estrogen. Thus, while the picture is not entirely clear, it seems likely that pregnancy per se exerts little influence on bone mineral content, at least under normal conditions. However, biochemical evidence of osteomalacia has been found in gravid women in whom low calcium intake is combined with the cultural practice of excluding sunlight exposure from the skin.

Placental transfer: in contrast to calcium, the calcitrophic hormones, parathyroid hormone and calcitonin do not appear to cross the placenta. The placenta transports calcium ions actively, making the fetus hypercalcemic relative to its mother, which in turn stimulates calcitonin release and perhaps suppresses parathyroid hormone secretion by the fetus. Comparison of maternal-cord values at birth makes it doubtful that the human placenta transports 1,25-dihydroxyvitamin D3 in vivo. Thus, the levels of total and ionic calcium in cord blood regularly exceed those in maternal blood by an average of 1 and 0.5 mEq/L, respectively. Magnesium is marginally higher and phosphorus substantially so, in cord blood as compared with maternal blood (Pikin et al, 1985). A unique extrarenal system for 1 a-hydroxylation of 25-hydroxyvitamin D3 exists in the placenta and/or decidua, providing a source of 1,25-dihydroxyvitamin D3 for the fetus. This capacity for 1 a-hydroxylation has been documented in vitro studies of the rat placenta and the human decidua and placenta.

At birth the neonate is certainly hypercalcemic, probably hypercalcitonemic, and perhaps hypoparathyroid. With placental separation, the previously abundant supply of calcium ceases abruptly and the infant's serum calcium level begins to fall, reaching a Nadir between 24 and 48 hours of age when it is about 1 mEq/L below that at birth. Thereafter, it rises slightly to stabilize at adult levels by 5 to 7 days of age. These changes involve both total and ionic forms of calcium.

The clinical aspects of calcium metabolism during pregnancy includes: hyperparathyroidism during pregnancy causes complications in both mother and infant and should be treated surgically as soon as diagnosed; maternal hypoparathyroidism can be treated satisfactorily with high doses of supplemental calcium and vitamin D.

osteopenia accompanying long-term heparin administration may respond to 1,25-dihydroxyvitamin D3 (Calcitriol) therapy.

Diabetes in pregnancy is associated with disturbed neonatal calcium homeostasis, perhaps due to chronic hypomagnesemia. There is no role of calcium in preterm delivery and premature rupture of fetal membranes as was previously suggested (Kurholma et al, 1984). A possible etiological role of calcium deficiency in pregnancy related hypertension has been suggested (This will be discussed in details in the next part).

Calcium and the Blood Pressure:

Intracellular calcium ions serve as the final common pathway through which the various factors involved in hypertension act. A rise in the intracellular calcium ion concentration immediately triggers a vascular smooth-muscle contraction. The steady-state intracellular calcium ion concentration determines the resting muscle tone. These two factors-the steady state intracellular Ca^{+2} concentration and changes in intracellular Ca^{+2} concentrations in response to a stimulus-are the final determinants in raising peripheral vascular resistance-a hallmark of systemic hypertension.

For the resting smooth-muscle cell, there is an enormous concentration gradient across the plasma membrane for calcium ions. Two factors help maintain the 5,000-10,000-fold calcium ion gradient across the plasma membrane: first, the resting membrane is only slightly permeable to calcium ions; second, there is a high-affinity, high-capacity Mg^{+2} ATPase-driven calcium pump to transport the Ca^{+2} out of the cell. Hence, hypertension may result from the excessive Ca^{+2} influx induced by greater

sympathetic nervous system activity or from the increased transmembrane Ca^{+2} influx caused by excessive humoral stimulation with a-adrenergic agents or angiotensin.

Intrinsic abnormalities in cell membrane transport or binding of calcium ions could also increase cytosol calcium concentrations and abnormally elevate vascular tone. If the increase of intracellular Ca^{+2} causes contraction of vascular smooth muscle, one can assume that the increase in extracellular Ca^{+2} (as by calcium supplementation) or the decrease in intracellular Ca^{+2} (as by calcium channel blockers) will lead to the relaxation of vascular smooth muscles.

In an epidemiological survey of blood pressure, highly significant positive correlation was found between serum calcium and both systolic and diastolic blood , and a significant but weaker correlation between urinary calcium excretion and blood pressure (Kesteloot and Geboeris, 1982). A new concept of the pathogenesis of hypertension combining the effect of sodium and calcium on blood pressure has evolved in the last few years. In subjects with a genetically determined predisposition to the development of hypertension, a high sodium consumption leads to a volume overload, which results in the appearance of a Saluretic hormone. This hormone influences membrane permeability which leads to an increase in intracellular sodium and by inhibiting the sodium calcium exchange causes accumulation of calcium in vascular smooth muscle cells. The increase in intracellular calcium would lead to an increased contractility and vascular tone, resulting in an augmented peripheral vascular resistance and consequently in raised blood pressure (Kesteloot and Geboers, 1982). These findings might also help to explain the beneficial role of calcium antagonists in the treatment of hypertension.

Calcium and Pregnancy Induced Hypertension:

It has been reported epidemiologically that the incidence of eclampsia in populations with a low calcium intake was high whereas populations with a high calcium intake such as Guatemalan and Ethiopian populations demonstrated a low incidence of eclampsia (Beligan et al, 1971). It has also been reported that the blood pressure in pregnant women can be reduced by oral calcium administration (Belizan et al, 1983). It has also been reported that normal pregnancy is associated with a loss of vascular responsiveness to the pressor effects of infused angiotensin II (Gant et al, 1973).

There is wide agreement that loss of vascular refractoriness to angiotension II plays one of the most important roles in the pathogenesis of pregnancy induced hypertension. It has been considered, therefore, that restoration of angiotensin II refractoriness may by some means be able to prevent the onset of pregnancy-induced hypertension, and researches along these lines are expected.

As the pregnant woman destined to develop pregnancy-induced hypertension loses refractoriness to the pressor effects of infused angiotensin II, the effect of calcium supplementation on the vascular sensitivity to angiotensin II was investigated in pregnant women by Kawasaki & Co. (Kawasaki et al, 1985). They found that the vascular sensitivity was significantly decreased after calcium supplementation. The incidence of pregnancy-induced hypertension in the calcium supplemented patients was 4.5% which was smaller than that in the nonsupplemented patients (21.2%).

They suggested that calcium supplementation tends to reduce the vascular sensitivity in pregnancy. Although there is no clear explanation of the mechanisms involved in such an effect of calcium, the present results do provide evidence to support the idea that oral calcium intake can prevent the onset of pregnancy-induced hypertension. Belizán (Belizán et al, 1983) suggested that one possible explanation of the effect of calcium on blood pressure involved parathyroid hormone, since a partial coefficient correlation between parathyroid hormone levels and diastolic pressure was observed. There is one other interesting observation which has a bearing on the possible explanation of the present results. Bohn (Bohn et al, 1963) found that a high calcium concentration depressed the vascular smooth muscle response, probably by binding to the muscle cell membrane, thereby stabilizing it, reducing it excitability, and inhibiting its contraction.

From the viewpoint of prevention, it does not seem to be necessary to reduce blood pressure. Therefore, ingesting adequate calcium may be valuable for preventing the onset of pregnancy-induced hypertension. Furthermore, Belizán and Co. (Belizán et al, 1983) have shown that calcium supplementation can reduce blood pressure of normal pregnant women. Both calcium-supplemented groups (with either 1 or 2 gm of calcium daily) tended to have reductions in systolic blood pressure in the second trimester, whereas pressures oscillated throughout gestation in the control group. In the third trimester, the systolic blood pressure increased in controls and in patients given 1 gm of calcium, but those given 2 gm of calcium experienced no rise in systolic pressure in the third trimester. Diastolic blood pressure showed similar trends,

remaining significantly lower in the latter part of pregnancy in the group given 2 gm of calcium.

No significant group deficiencies in calcium and phosphorus levels were noted, nor were changes in parathyroid hormone concentration significant.

In a study population that comprised 34 normal black pregnant women, biochemical changes were, compared between a group of women who received 1.5 gm of calcium supplementation a day and a group of women who received placebos. The blood pressure-lowering effect of calcium supplementation appears to involve a mechanism that relates parathyroid hormone and plasma renin activity. Other alterations in calcium and magnesium metabolism, as reflected by increased urinary calcium excretion and serum magnesium levels, may also contribute to this effect. Subgroups of study participants with initial (<26 weeks' gestation) low levels of serum calcium and plasma renin activity are the ones with the largest reductions in blood pressure. Whether these alterations can produce a reduction in the incidence of pregnancy-induced hypertension is the next question to be answered in this area. (Repke et al, 1989).

These findings support the hypothesis that calcium supplementation reduces blood pressure in pregnant women. Regardless of the mechanisms involved, it is clear that low calcium levels are associated with elevated blood pressure. Calcium supplementation also reduces blood pressure in non-pregnant women and in animals.