SEROTONIN-2-RECEPTOR BLOCKERS AND PREECLAMPSIA

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Introduction

Preeclampsia is a multisystem disorder affecting virtually every organ and system in the body, with hypertension and proteinuria, the traditional diagnostic features, representing two facets of a complex pathophysiological process. The common pathological feature of the disease, whether in the decidual vessels of the placental bed, renal microvasculature, liver, heart or cerebral circulation, is vascular endothelial damage and dysfunction. Causes leading to the changed endothelial activation in preeclampsia remain the subject of investigation (1). Endothelial dysfunction is well documented in the uteroplacental and decidual vessels (1).

When compared to normal pregnancy, endovascular trophoblast invasion is shallow and physiologic changes in spiral artery vessel wall are for the greater part absent. The same pathological changes are observed in placentas from small for date (2). This association leads to the suggestion that some cases of fetal growth restriction differ from preeclampsia only in the maternal response to a shared placental pathology. Endothelial activation occurs in response to abnormal placentation, which leads to placental ischemia and the release of placental factors that activate the maternal endothelium. Maternal endothelium is the target organ in preeclampsia. There is both structural (3) and functional evidence for endothelial dysfunction in preeclampsia (4). The placental problem causes both maternal and fetal syndromes (5). The balance of the two syndromes varies: in some cases there is a major fetal problem and in other cases maternal problems dominate the clinical picture. The link between abnormal placentation and the maternal and fetal syndromes is incompletely disclosed. Dysfunctional endothelial cell activation is associated with the characteristics of preeclampsia; vasospasm, increased capillary permeability and platelet aggregation (1). Under normal circumstances endothelial forms a smooth non-thrombogenic surface lining the blood vessels. Endothelial cells are involved of initiation and promotion of coagulation. The endothelial cell dynamically balances these opposing

functions via modulation of platelet activation, clot formation and fibrinolysis. Normal endothelial function should be distinguished from endothelial dysfunction. Endothelium is involved in the clinical manifestations of preeclampsia. The nature of this endothelial involvement in preeclampsia is less clear. Endothelial activation is usually an appropriate and reversible response to several different stimuli and this process is quite physiological. If activation occurs inappropriately it can result in transient or irreversible vascular injury. The response of the activated endothelial cell is dysfunctional and may lead to uncontrolled coagulation, platelet aggregation and activation, vasoconstriction and impaired permeability. Endothelial injury refers to physical disruption of the endothelial lining (6).

Serotonin and preeclampsia

Platelets play a central role in the disease process of preeclampsia. Platelet activation is a physiological feature of a healthy pregnancy, and is exaggerated in preeclampsia (7). There is considerable evidence implicating platelet activation in the pathophysiology of preeclampsia. Thrombocytopenia is the most frequent hemostatic abnormality in established preeclampsia but platelet count may vary greatly (8;9). Platelets adhere to abnormal endothelial cells and become activated. Because platelets are the principal source of circulating serotonin the increased platelet aggregation in women with preeclampsia causes an increase in serotonin levels. Elevated levels of serotonin and enhanced sensitivity to serotonin are reported in normal pregnancy and are highly increased in preeclampsia. These findings indicate an altered metabolism of serotonin during pregnancy and suggest a possible role of serotonin in the pathophysiology of preeclampsia (10;11). Significantly higher levels of serotonin were reported in platelet-poor plasma, serum, urine and placentas of women with preeclampsia (12-17). Platelet serotonin concentration was shown to be reduced in women with preeclampsia (10;18). Serotonin has been implicated in causing increased vascular permeability(10). Interaction of serotonin with serotonin-1-receptor or serotonin-2- receptor depends on the state of the endovascular trophoblast or endothelium in the spiral arteries and has opposite effects with regard to vasodilatator and vasoconstrictive influences. Serotonin-induced vasodilatation is mediated by specific endothelial serotonin-1-receptors and a subsequent endothelial release of prostacyclin and nitric oxide. In vascular diseases that are characterized by endothelial dysfunction and loss of endothelial serotonin-1-receptors serotonin will

react with the serotonin-2-receptors which are located on vascular smooth muscle cells and platelets. Stimulation of these serotonin-2-receptors results in direct vasoconstriction and platelet aggregation. Furthermore, the effects of other vasoconstrictive agents as catecholamines and angiotensin-II are enhanced. Because preeclampsia is characterized by inappropriate endothelial activation and platelet aggregation selective blockade of the effects of serotonin that are mediated by binding to the serotonin-2-receptor may provide an attractive pharmacotherapeutic option in the management of severe preeclampsia. Blockade of the serotonin-2-receptor with a serotonin-2-receptor antagonist may counteract serotonin-dependent vasoconstriction and increased platelet aggregation, which are both characteristics of preeclampsia.

Serotonin-2-receptor blockers for preeclampsia

Ketanserin is a selective serotonin-2-receptor blocker, with some degree of α_1-blocker activity and it is a potent platelet aggregation inhibitor. The main pharmacological actions of ketanserin are: 1) selective inhibition of serotonin-induced vasoconstriction but not of serotonin-induced vasodilatation; 2) inhibition of serotonin-induced amplification of vasoconstriction by other vasoactive agents; 3) selective inhibition of serotonin-induced platelet aggregation; 4) inhibition of serotonin-induced augmentation of platelet aggregation by other vasoactive agents; 5) at concentrations significantly higher than needed for serotonin-2 antagonism, α_1-adrenergic blockade occurs.

Because of these properties it was supposed that ketanserin could be an attractive candidate agent for treatment of preeclamptic hypertension. The effect of ketanserin on the hemodynamic profile in severe early onset preeclampsia was addressed in two studies including a total of 35 patients(19;20). Ketanserin induced a rapid but gradual decrease in blood pressure and a moderate drop in systemic vascular resistance without a significant change in cardiac output (19). Studies comparing intravenous ketanserin and (di)hydralazine were mainly performed in the Netherlands and South Africa. Ketanserin was shown to gradually decrease blood pressure, with minimal risk of hypotensive overshoot. Significantly fewer maternal complications and side effects were found (21-23).

The optimal dose of ketanserin for use in pregnancy has to be established (24). Out of a number of variables total body weight was the only significant variable to influence

the pharmacokinetics of ketanserin in preeclamptic patients. [Yassen A, Hanff LM, Vermes A, Visser W, Mathot R, Vulto AG. Population pharmacokinetics of ketanserin in pre-eclamptic patients. (abstract) Hypertens Pregn 2002;21suppl.1:40]. Thus far all studies reported found that intravenous ketanserin is a safe drug in the management of established preeclampsia with beneficial maternal outcomes and no harmful fetal effects (25).
A recent meta analysis concluded that the most promising agents to replace hydralazine, but requiring further investigation, are nifedipine and labetalol or ketanserin if it is available locally (26).

Serotonin-2-receptor blockers and prevention of preeclampsia

Placental microcirculation is disturbed in preeclampsia. It has been demonstrated that serotonin-2-receptor blockers have a favorable effect on the microcirculation of organs under pathological conditions. In theory ketanserin can be beneficial for the microcirculation in pregnancy, however, this has not been investigated for the placenta. Steyn and Odendaal after randomization for ketanserin or placebo reported a decrease of the risk of superimposed preeclampsia and also a significantly higher birth weight in the group receiving ketanserin(27). Throughout pregnancy no adverse effects on fetal heart rate monitoring were noted(28). Ketanserin crosses the placenta. Recently a six year follow-up study of the children after in utero exposure to oral ketanserin or placebo was presented and did not find any differences with regard to height, weight, head circumference or mental development [Steyn DW, Odendaal HJ, Kirsten GF. Mental Development of Children Six Years After in Utero Exposure to Ketanserin_A follow-up Study of a randomized Controlled Trial. (abstract) Hypertens Pregn 2002;21suppl.1:131]. Prevention of preeclampsia and intrauterine growth restriction with oral ketanserin is addressed in a case report in which two women are their own controls with regard to ketanserin administration(29).

Conclusion

Intravenous ketanserin is a useful drug for treating established preeclampsia with beneficial effects on the maternal disorder and no harmful fetal effects. The possible role of ketanserin in prevention of preeclampsia and intrauterine growth restriction requires further investigation.

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