Available online at www.sciencedirect.com
ScienceDirect
European Journal of Obstetrics & Gynecology and Reproductive Biology 128 (2006) 199–203
ejog European Journal of Obstetrics & Gynecology and Reproductive Biology
www.elsevier.com/locate/ejogrb

Insufficient efficacy of intravenous ketanserin in severe early-onset pre-eclampsia

Lidwien M. Hanff [a,*], Willy Visser [b], Danielle W.E. Roofthooft [c], Andras Vermes [a], Wim C.J. Hop [d], Eric A.P. Steegers [b], Arnold G. Vulto [a]

[a] *Department of Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam, The Netherlands*
[b] *Department of Obstetrics and Gynaecology, Erasmus University Medical Centre, Rotterdam, The Netherlands*
[c] *Department of Neonatology, Erasmus University Medical Centre, Rotterdam, The Netherlands*
[d] *Department of Biostatistics and Epidemiology, Erasmus University Medical Centre, Rotterdam, The Netherlands*

Received 24 August 2005; received in revised form 9 November 2005; accepted 22 November 2005

Abstract

Objective: To analyze the efficacy of intravenous ketanserin in controlling blood pressure of severe early-onset pre-eclamptic patients.
Study design: Pre-eclamptic patients ($n = 47$) with a gestational age (GA) between 21 and 32 weeks were treated with intravenous ketanserin in a maximum dosage of 14 mg/h, to obtain a diastolic blood pressure of 90 mmHg or below. The number of patients reaching and maintaining target blood pressure was retrospectively assessed. Patient characteristics associated with an adequate or inadequate response to ketanserin treatment were identified.
Results: With a maximum intravenous dosage of ketanserin, target blood pressure was not achieved in 15 (32%) patients. A high systolic blood pressure at the start of treatment was significantly ($p = 0.02$) associated with failure of ketanserin treatment.

The median period of ketanserin treatment in the responding group was 3 days (range 1–10 days). In 26 (55%) of initially successfully treated patients, additional antihypertensive drugs had to be added to maintain adequate blood pressure control.
Conclusion: Intravenous ketanserin lacks antihypertensive efficacy in a substantial proportion of severe pre-eclamptic patients, despite high dosages. In patients who initially respond well to ketanserin treatment, additional antihypertensive treatment is often necessary to maintain adequate blood pressure control.

Keywords: Pre-eclampsia; Ketanserin; Efficacy; Antihypertensive treatment

1. Introduction

The mainstay of treatment of pre-eclampsia is to lower the elevated blood pressure in order to prevent maternal complications like cerebrovascular hemorrhage and organ damage. In early-onset pre-eclampsia, adequate antihypertensive treatment can also yield sufficient time to administer antenatal steroids in order to improve neonatal outcome. In recent years, temporizing management with antihypertensive drugs is increasingly applied in patients with early-onset pre-eclampsia as long as both maternal and fetal condition permits [1–3].

The use of the serotonin (5HT)-antagonist ketanserin for antihypertensive treatment of pre-eclampsia has increased in the past years. The drug acts by blocking the vasoconstrictive response upon binding of 5HT to $5HT_{2A}$ receptors in vascular tissue [4]. Because of its inhibitory effect on platelet aggregation, ketanserin is thought to have an additional beneficial effect in patients with HELLP-syndrome (haemolysis, elevated liver enzymes, low platelet-count) [5].

There are conflicting data on the efficacy of ketanserin in pre-eclampsia. Bolte et al. [6] showed that ketanserin resulted

* Corresponding author at: Erasmus MC Rotterdam, Department of Hospital Pharmacy, Dr. Molewaterplein 40, 3015 GD Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, Netherlands. Tel.: +31 10 4633202; fax: +31 10 4366605.
E-mail address: l.hanff@erasmusmc.nl (L.M. Hanff).

0301-2115/$ – see front matter
doi:10.1016/j.ejogrb.2005.11.032

in a better blood pressure control and less maternal side effects than dihydralazin. However, the dosage of dihydralazin was low and the patients treated with ketanserin needed antihypertensive co-medication to maintain adequate blood pressure control. Rossouw et al. [7] compared short-term antihypertensive treatment with ketanserin and dihydrazin in a group of 80 patients with severe hypertension in the third trimester of pregnancy and found a better antihypertensive response with dihydralazin. However, ketanserin has the advantage of causing a more gradual decline in blood pressure than dihydralazin [6], which may reduce the risk of fetal distress. Ketanserin is one of the few drugs in the Netherlands licensed for pre-eclampsia in patients with a diastolic blood pressure of 110 mmHg or higher and has become the drug of choice to stabilize pre-eclamptic patients.

In 1999 we started using ketanserin as a first line treatment in our hospital for severe early-onset pre-eclampsia with the aim to control blood pressure and prolong pregnancy, as long as maternal and fetal condition allow. Because of the conflicting data on the efficacy of ketanserin and the need for clinical evaluation of the use of ketanserin in a population of severe early-onset pre-eclamptic patients, we performed a retrospectively analysis of the use of ketanserin, in terms of its efficacy in controlling blood pressure.

2. Materials and methods

Patients who were admitted to the antenatal High Care ward in the period 1999–2002 with severe early-onset pre-eclampsia (GA between 20 and 32 weeks on admission) were included in this evaluation. Severe pre-eclampsia was defined as the occurrence after 20 weeks of gestation of a diastolic blood pressure $\geq$110 mmHg (Korotkoff V) and proteinuria $\geq$0.3 g/24 h or the occurrence of a repetitive diastolic blood pressure $>$90 mmHg in combination with the HELLP-syndrome. HELLP syndrome was defined as the simultaneous occurrence of ALAT and/or ASAT $>$ 31 U/l (2 S.D. above the mean in our hospital), platelet count below 100×10^9 U/l and haptoglobin below 0.28 g/l (normal value 0.28–2.01 g/l).

Each woman received a radial arterial line for intra-arterial blood pressure measurement and a central venous line for central venous pressure (CVP) measurement.

Antihypertensive treatment was continued as long as fetal and/or maternal condition did not warrant delivery, as judged by the attending obstetrician. Fetal condition was assessed using cardiotocography (CTG) after a gestational age of 26 weeks or more.

2.1. Drug treatment

Drug treatment was targeted at achieving an intra-arterial diastolic blood pressure of 90 mmHg or below (with a lowest limit of acceptance of 75 mmHg).

After a bolus injection of 5 mg, the infusion rate of ketanserin (Ketensin®, Pharmacia, Woerden, the Netherlands) was initiated at 4 mg/h and increased, according to the blood pressure, with 2 mg/h every 20 min to a maximum of 14 mg/h. Each increment was preceded by an intravenous loading bolus injection of 5 mg ketanserin. Patients, who were already taking oral antihypertensive drugs on admission (methyldopa and/or nifedipine) continued these medications at their established dosage regime.

The goal was to reach the desired intra-arterial diastolic blood pressure using the titration schedule with ketanserin to a maximum of 14 mg/h. If the desired blood pressure could not be obtained using the maximum dosage of ketanserin, oral antihypertensive drugs (methyldopa to a maximum of 4 g daily or nifedipine to a maximum of 90 mg daily) and subsequently parenteral dihydralazin (starting with 1 mg/h to a maximum of 12 mg/h) or parenteral nicardipin (starting with 1 mg/h to a maximum of 10 mg/h) were started.

CVP was maintained at 5–6 mmHg, using pasteurized plasma-solution. All patients received antenatal steroids after 26 weeks of gestation.

2.2. Data analysis

The efficacy of ketanserin treatment was assessed by analyzing the proportion of patients that reached the target blood pressure with ketanserin (responding group) and the group of patients that did not reach target blood pressure (non-responding group), despite the maximum dosage of ketanserin. The responding and non-responding groups were compared with respect to differences in initial patient characteristics (diastolic and systolic blood pressure and gestational age at the start of treatment), using the Mann–Whitney *U*-test. Additionally, both groups were compared with respect to the use of oral antihypertensive drugs at start of treatment and diagnosis of HELLP-syndrome at start of treatment, using the Chi-square test. Statistical analysis was performed using SPSS (version 10.1, SPSS Inc, Chicago, USA). Safety of ketanserin treatment was determined as the absence of hypotensive periods during treatment (defined as an intra-arterial diastolic BP $<$ 70 mmHg) as well as assessment of maternal adverse effects, as reported in the patient charts. Fetal and neonatal outcome was assessed in terms of IUFD, neonatal death, number of severely growth restricted neonates at birth, pH-value umbilical artery, number of neonates with an APGAR score $<$7 at 5′, number of neonates admitted to ICU, days of artificial ventilation and number of neonates with hypotension within 24 h after birth, needing treatment.

3. Results

Forty-seven patients between 1999 and 2002 were admitted with severe early-onset pre-eclampsia to the high care obstetric ward and treated with intravenous ketanserin.