Ketanserin versus dihydralazine in the management of severe early-onset preeclampsia: Maternal outcome

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OBJECTIVE: An open, randomized, prospective, multicenter trial was conducted to compare the efficacy and safety of intravenous ketanserin, a selective serotonin 2 receptor blocker, with that of intravenous dihydralazine in the management of severe early-onset (<32 weeks' gestation) preeclampsia. End points of this study were blood pressure control and maternal outcome.

STUDY DESIGN: Patients with a diastolic blood pressure >110 mm Hg were randomly assigned to receive either ketanserin (n = 22) or dihydralazine (n = 22) as initial therapy. Plasma volume expansion preceded antihypertensive treatment, which was administered according to a fixed schedule.

RESULTS: The reductions in blood pressure with the 2 drugs were similar; however, adequate blood pressure control was reached significantly earlier with ketanserin (84 ± 63 vs 171 ± 142 minutes, $P = .017$). Occurrence of maternal complications was significantly lower among patients who received ketanserin than among patients who received dihydralazine (n = 6 vs n = 18, $P = .0007$). A significant difference in favor of ketanserin was noted in daily fluid balance.

CONCLUSION: Antihypertensive efficacies of ketanserin and dihydralazine were comparable, but significantly fewer maternal complications were noted among the patients receiving ketanserin. Ketanserin is an attractive alternative in the management of severe early-onset preeclampsia. (Am J Obstet Gynecol 1999;180:371-7.)

Key words: Dihydralazine, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, ketanserin, maternal outcome, preeclampsia

Severe early-onset preeclampsia is an infrequent but serious maternal disease for which the only cure is removal of the trophoblast, which means ending the pregnancy.[1] However, iatrogenic preterm delivery increases the risk of adverse neonatal outcome. Prolongation of pregnancy is theoretically favorable for the fetus, whereas it remains controversial whether maternal condition is further jeopardized by expectant management.[2, 3] Expectant management in cases of HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome is even more controversial.[4, 5] Therapy consisting of plasma volume expansion and pharmacologic vasodilation, often combined with anticonvulsant drugs, and accompanied by close monitoring of the maternal and fetal conditions has been advocated by several authors.[6, 7]

Hydralazine or dihydralazine is the antihypertensive drug most commonly used in the management of severe preeclampsia, but it has some well-known drawbacks.[8, 9] Ketanserin is a serotonin 2 receptor antagonist with some dose-dependent central and peripheral α_1-adrenergic receptor antagonistic activity. Earlier peripartum studies in hypertensive patients showed that effective blood pressure control could be obtained with the use of ketanserin.[10, 11] In this study ketanserin and dihydralazine were compared with respect to their antihypertensive efficacies and associated maternal outcomes.

Material and methods

An open, randomized, prospective trial with 2 parallel groups was conducted in 4 hospitals. Approval of the study was obtained from the medical scientific and ethical committees of the participating hospitals. If a patient fulfilled the selection criteria and provided written, informed consent, block randomization was carried out with the centers as strata. A central telephone number was dialed to reach an answering service that provided the medication assignment.

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Table I. Clinical characteristics at admission

	Ketanserin (n = 22)		*Dihydralazine (n = 22)*	
	Mean or No.	*SD or %*	*Mean or No.*	*SD or %*
Systolic blood pressure (mm Hg)	172	13	175	19
Diastolic blood pressure (mm Hg)	122	8	123	8
Age (y)	26.5	4	28.7	5
Gestational age (d)	206	13	201	10
Nulliparous	21	95	17	77
Proteinuria >0.3 g/24 h	12	55	17	77
Chronic hypertension	4	18	3	14
Clinical symptoms	10	45	13	59
Antihypertensive drugs*	3	14	3	14
HELLP syndrome	2	9	3	14
Eclampsia	1	5	1	5

Values for continuous variables are mean ± SD; values for categoric variables are number and percentage of patients.
*Oral antihypertensive medication continued during trial.

Inclusion criteria were as follows: repeated diastolic blood pressure measurements (Korotkoff sound 4, sphygmomanometer) >110 mm Hg in previously normotensive patients or an elevation of diastolic blood pressure by ≥20 mm Hg compared with measurements before 20 weeks' gestation in patients with chronic hypertension, gestational age between 26 and 32 weeks, and fetal condition that permitted prolongation of pregnancy, as demonstrated by a reassuring fetal heart rate tracing. Patients with fetal growth restriction, as judged by ultrasonographic examination, and patients with abnormal umbilical artery Doppler flow velocity waveforms were also included. Antihypertensive medications other than ketanserin or dihydralazine taken by the patients before random assignments were continued during the study period. Maternal exclusion criteria were history of cardiac disease or arrhythmias, serum aspartate aminotransferase or alanine aminotransferase activity >250 IU/L, and evidence of overt disseminated intravascular coagulation.

It was hypothesized that ketanserin, in preventing serotonin-induced vasoconstriction and platelet aggregation, not only would be adequate in lowering blood pressure but would have a beneficial effect on the basic disease process. Sample size estimates were based on the results of a pilot study. On the assumption that a difference of 3 days of extra pregnancy prolongation with SD of 3 days would occur between ketanserin and dihydralazine, it was calculated that a total of 34 patients (17 per treatment group) would be required to detect this difference at the 5% significance level (2-tailed) with 80% power.

Forty-four patients were included in the study, all with singleton pregnancies and not in labor; 22 were assigned to receive ketanserin as initial therapy and 22 were assigned to receive dihydralazine. Plasma volume was expanded with 750 mL plasma colloid substitute, modified fluid gelatin 4% solution in normal saline solution (Gelofusine; Vifor BV, Huizen, The Netherlands). Thirty patients (ketanserin, n = 14; dihydralazine, n = 16) had a pulmonary artery catheter inserted and underwent radial artery cannulation. In these patients a reduced circulating volume was expanded with plasma colloid substitute until a pulmonary capillary wedge pressure of 10 ± 2 mm Hg was reached. If diastolic blood pressure after plasma volume expansion was not within a predefined range (70-95 mm Hg for intra-arterial measurement or 85-110 mm Hg measured with a sphygmomanometer), the assigned antihypertensive therapy was started. Otherwise, the medication was started as soon as diastolic blood pressure again rose to values outside the target range. All patients in the study received medication.

Antihypertensive medication was administered according to a fixed scheme. Patients in the ketanserin group received an intravenous bolus of 5 mg and a starting dose by continuous infusion of 4 mg/h. The dose was increased every 20 minutes until target blood pressure was reached. A 5-mg bolus of ketanserin was given at each 2-mg/h dose increment. Dihydralazine was started at a continuous infusion rate of 1 mg/h, with hourly increments of 1 mg until target blood pressure was reached. The maximum dose for both drugs was 10 mg/h. When the maximum dose of initial medication was not sufficient to reach or maintain target blood pressure, the other medication was given as add-on therapy. Likewise, dose was increased or reduced by a fixed regimen in case of a recurrent increase in blood pressure after a period of stabilization or in case of hypotensive overshoot. Magnesium sulfate was used in 8 patients in the ketanserin group and 11 in the dihydralazine group; it was given only to patients with signs of impending eclampsia. Thirty-eight patients, 19 in each treatment group, received steroids for acceleration of fetal lung maturation. Of the 7 patients with chronic hypertension who were enrolled in the study, 6 had significant proteinuria (>0.3 g/24 h); proteinuria was no longer detectable 6 weeks post partum in 5 of these patients. There were 6 multiparous patients included, 3 of whom were pregnant with a new partner after previous uncom-

Table II. Maternal outcomes

	Ketanserin	*Dihydralazine*	*Significance**
Time to target diastolic blood pressure (min)	84 ± 63	171 ± 142	*P* = .017
Diastolic blood pressure target not reached	0	3	
Add-on medication	10	2	*P* = .016
Prolongation (d)	5.8 ± 4.6	6.5 ± 4.9	
Symptoms†			
Headache	4	11	*P* = .027
Visual complaints	0	4	*P* = .048
Epigastric pain	3	2	
Nausea and vomiting	2	9	*P* = .016
Malaise	3	9	*P* = .045
Delivery indication			
Maternal	4	7	
Fetal	13	11	
Combined maternal and fetal	5	3	
Complications			
HELLP syndrome	2	10	*P* = .016
Oliguria	2	9	*P* = .034
Pulmonary edema	0	4	*P* = .049
Eclampsia	0	1	
Disseminated intravascular coagulation	1	0	
Abruptio placentae	0	4	
Maternal death	0	1	

Values are mean ± SD for continuous variables and number of patients for categoric variables.
*Given only when $P < .05$.
†Clinical symptoms with monotherapy during first 2 days of therapy.

plicated pregnancies. At admission 5 patients had HELLP syndrome, defined as platelet count < 100×10^9 cells/L, aspartate aminotransferase or alanine aminotransferase activity > 70 IU/L, and lactate dehydrogenase activity >600 IU/L or bilirubin level >17 μmol/L.[12]

Management included unrestricted diet and modified bed rest. Maternal condition was assessed by recording of blood pressure at preset intervals, daily fluid balance calculations, daily laboratory evaluation, and observation of maternal well-being. Maternal well-being was assessed at start of therapy and each morning thereafter by patients themselves on a 4-point scale (*1,* bad; *2,* moderate; *3,* good; *4,* excellent), and patients were instructed to report development of cerebral or visual disturbances and epigastric or right upper quadrant pain. Complaints such as anxiety, agitation, nervousness, and tightness of the chest were grouped as feelings of general malaise. Concomitant medications were listed. Maternal outcome parameters included oliguria (mean output <40 mL/h in 24-hour urine collection), de novo development of HELLP syndrome, eclampsia, pulmonary edema, disseminated intravascular coagulation, abruptio placentae, and maternal death. Fetal condition was monitored frequently. The decision to deliver the patient, whether by cesarean delivery or by induction, was made by the attending obstetrician. The reason for discontinuation of pregnancy was noted. Reasons for discontinuation of the trial other than delivery were the attainment of 34 weeks' gestation or an aspartate aminotransferase or alanine aminotransferase activity >500 IU/L after 3 days of treatment. Postpartum complications were recorded.

Statistical analyses were performed with the Fisher exact test for nominal data and the unpaired Student *t* test or Mann-Whitney *U* test for parametric and nonparametric data as appropriate. When a 4-point scale was used (for well-being and clinical complaints), ordinal ratings were given numeric values 1 through 4, mean and SD were calculated, and the Wilcoxon signed rank sum test was used to analyze the differences within groups. Results are presented as incidence or as mean and SD unless otherwise stated. $P < .05$ for a 2-tailed test was considered statistically significant.

Ketanserin was supplied by Janssen-Cilag BV (Tilburg, The Netherlands).

Results

Relevant clinical characteristics at inclusion, as shown in Table I, were comparable between the 2 treatment groups. The results of blood pressure, heart rate, and well-being measurements are for patients receiving intravenous monotherapy, whereas fluid balance and peripartum complications concern patients receiving initial therapy and, when necessary, add-on therapy. Table II summarizes the main end points of this study. In both groups pregnancy was prolonged for 6 days. Neonatal outcomes were comparable with respect to morbidity and mortality rates.

Blood pressures were reduced to similar levels with both drugs. Diastolic blood pressure course is depicted in Fig 1, as is mean heart rate, which was significantly increased with dihydralazine. The time required to achieve the predefined diastolic blood pressure range was significantly shorter for patients receiving ketanserin (mean

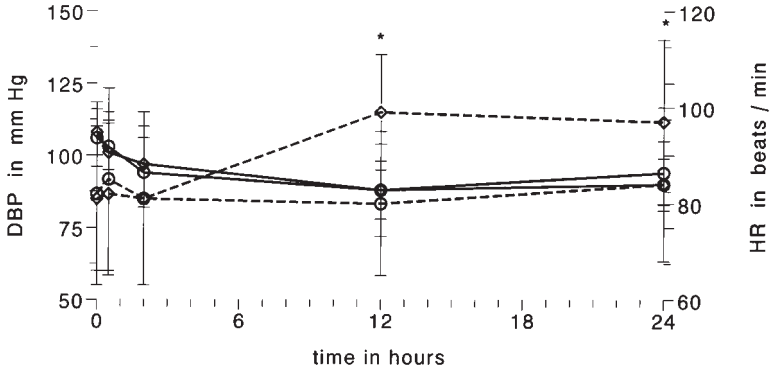

Fig 1. Effects of ketanserin monotherapy *(circles)* and dihydralazine monotherapy *(diamonds)* on diastolic blood pressure *(DBP)* are depicted by *solid lines,* and their effects on heart rate *(HR)* are depicted by *broken lines.* Each *point* represents mean value with *bars* representing SD of mean. *Asterisk,* Significant difference in heart rate between 2 treatment groups ($P < .05$).

and SD 84 ± 63 minutes) than for patients receiving dihydralazine (171 ± 142 minutes, $P = .017$). The addition of the alternate medication to the therapeutic regimen, however, occurred with a significantly higher frequency in the ketanserin group, 10 times versus 2 times ($P = .016$). In 8 of these 10 cases the addition of dihydralazine to the ketanserin administration was for only a few hours (10 ± 6 hours). Hypotensive overshoots or other adverse effects required 9 dose reductions in 6 patients in the ketanserin group, whereas dihydralazine dose had to be reduced 28 times in 15 patients ($P > .05$).

Patients were asked to rate their feeling of well-being at start of therapy and daily thereafter on a 4-point scale: patients receiving dihydralazine felt significantly worse than baseline on days 3 and 4 of treatment. The initial mean score of 2.16 ± 0.83 changed to 1.75 ± 0.62 ($P = .031$) and 1.60 ± 0.70 ($P = .0078$) on days 3 and 4, respectively. Such a deterioration in well-being did not occur after initiation of ketanserin administration. With respect to the specific symptoms that patients were instructed to report, neither the number of patients with symptoms nor the number of times that the separate symptoms were mentioned differed significantly between the groups at inclusion. Table II shows the number of patients receiving monotherapy who reported such manifestations during the first 2 days of treatment. The number of patients requiring medication (sedatives, paracetamol, antiemetics) for these signs and symptoms was significantly higher in the group receiving dihydralazine than in the group receiving ketanserin (n = 17 versus n = 7, $P = .0058$). The numbers of times medication was taken in connection with these complaints were also significantly different in favor of the ketanserin group (0.5 ± 0.9 times versus 4.1 ± 5.6 times, $P = .002$).

The total numbers of maternal complications ($P = .0005$) and the numbers of patients with these complications ($P = .0007$) were 28 complications in 18 patients assigned to receive dihydralazine initial treatment and 7 complications in 6 patients assigned to receive ketanserin initially. When patients who received only ketanserin without add-on therapy with dihydralazine (n = 12) were analyzed against those who received dihydralazine at any time in therapy (n = 32), a significant difference in favor of ketanserin was seen in the numbers of patients with antepartum or postpartum complications (n = 3 vs n = 21, $P = .0212$). Apart from oliguria (which was only checked antepartum) and some cases of HELLP syndrome, many of the maternal complications occurred postpartum.

Six patients used oral antihypertensive agents (labetalol, n = 5, and α-methyldopa, n = 1). The 3 patients who were both using oral medication and receiving ketanserin had no complications; of the 3 patients who were both using oral labetalol and receiving dihydralazine, HELLP syndrome developed in 1 and 1 had abruptio placentae. Invasive hemodynamic monitoring did not influence maternal outcome. Patients both with and without invasive hemodynamic monitoring showed significantly more maternal complications in the dihydralazine group.

The 3 patients with HELLP syndrome at inclusion and dihydralazine as initial therapy still had HELLP syndrome at delivery. In addition 5 other patients receiving dihydralazine acquired HELLP syndrome antepartum, and HELLP syndrome occurred in 2 more at <3 days postpartum. HELLP syndrome was present at inclusion in 2 patients in the ketanserin group; both cases resolved before delivery. One patient receiving ketanserin acquired HELLP syndrome on day 3 of treatment; this resolved before delivery. Another patient receiving ketanserin acquired HELLP syndrome and was subsequently delivered. De novo development of HELLP syndrome at delivery or post partum thus occurred in 7 patients in the dihydralazine group and in 1 patient in the ketanserin group ($P = .017$). The total numbers of patients with HELLP syndrome occurring or persisting during treatment at deliv-

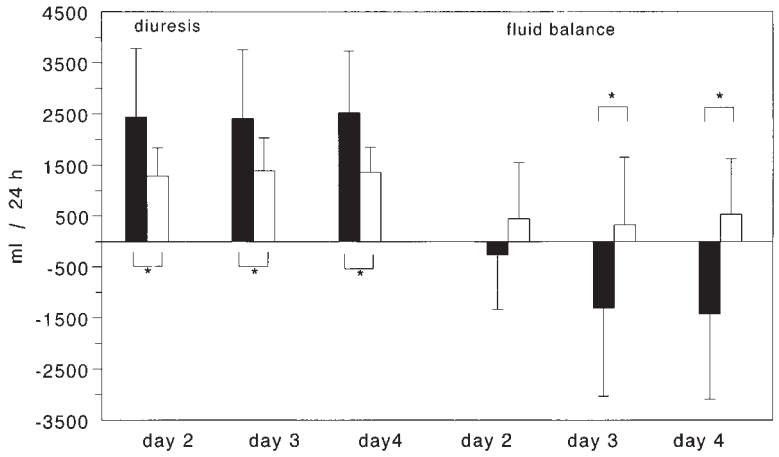

Fig 2. 24-Hour urinary output and fluid balance data for first 3 whole days, from midnight to midnight, in ketanserin group *(filled bars)* and in dihydralazine group *(open bars)*. Each *bar* represents mean value and is depicted as mean ± SD. *Asterisk,* Significant difference between 2 treatment groups ($P < .05$).

ery or post partum were 10 in the dihydralazine group and 2 in the ketanserin group ($P = .016$).

All patients were delivered by the cesarean route, without significant difference in reasons for pregnancy termination between the 2 groups (Table II). In 3 patients in the ketanserin group and 13 patients in the dihydralazine group, postpartum complications related to preeclampsia were found ($P = .004$). Four patients in the dihydralazine group acquired postpartum pulmonary edema, as opposed to none in the ketanserin group ($P = .049$). In the dihydralazine group there was 1 maternal death, 1 patient acquired a hemolytic uremic syndrome, and an eclamptic seizure occurred in 1 patient. Some patients in the dihydralazine group had >1 postpartum complication. Only 3 patients in the ketanserin group had postpartum complications. These were 1 case of therapy-resistant hypertension, 1 case of disseminated intravascular coagulation, and 1 case of temporarily increased serum creatinine concentration (peak value 234 μmoL/L).

The amounts of plasma colloid infused to correct depleted circulating volume before administration of antihypertensive medication were comparable in the 2 groups (1012 ± 529 mL in the ketanserin group and 981 ± 920 mL in the dihydralazine group). There was no significant differences between the groups in the urinary output during the period of plasma volume expansion. The mean amounts of fluid infused from start of medication until midnight were comparable (1398 ± 1394 mL in the ketanserin group and 1172 ± 1254 mL in the dihydralazine group), but diuresis differed significantly between the 2 groups (156 ± 186 mL/h in the ketanserin group and 93 ± 108 mL/h in the dihydralazine group, $P = .029$). This difference remained significant during the next days of treatment. Oliguria developed in 2 patients in the ketanserin group and in 9 patients in the dihydralazine group ($P = .034$). The data on diuresis and 24-hour fluid balance are presented in Fig 2.

Comment

Management protocols for dealing with severe preeclampsia emphasize timely referral to a perinatal center at which close fetal and maternal monitoring is available.[13] Two randomized clinical trials comparing aggressive and expectant management in severe preeclampsia remote from term demonstrated favorable neonatal outcomes in the expectant management group, whereas the number of maternal complications was not increased by expectant management.[14, 15] In a retrospective study Oláh et al[3] also found fewer neonatal complications; however, they noted a higher incidence of HELLP syndrome among patients whose preeclampsia was managed conservatively. Thus the management of patients with severe preeclampsia remote from term remains highly controversial, and neonatal outcome may benefit in some selected cases when prolongation of pregnancy is shown to be possible with a therapy that is safe and associated with as few as possible maternal risks.

Although hydralazine or dihydralazine is the preferred antihypertensive agent for the treatment of severe hypertension in pregnancy and experience with its administration in pregnancy is extensive, side effects have long been recognized as undesirable and may affect 50% of patients.[16] Side effects of dihydralazine include flushing, nasal congestion, headaches, tachycardia, restlessness, hyperreflexia, oliguria, tremulousness, nausea, and vomiting.[9, 16] The main problem with these side effects is their resemblance to the signs of deteriorating preeclampsia. Another adverse effect is the regular occurrence of hypotensive overshoot, which may cause serious fetal distress,

especially in fetuses with intrauterine growth restriction.[8]

Increased plasma and placental serotonin levels and impaired catabolism of placental serotonin have been documented in preeclampsia.[17, 18] Serotonin has been implicated in causing increased vascular permeability, in eliciting renal ischemia and subsequent renal cortical necrosis, and in enhancing vascular sensitivity to such vasoconstrictive agents as catecholamines and angiotensin II.[19, 20] Depending on the integrity of the vascular endothelium, interaction with serotonin results in vasodilation or vasoconstriction. If there is some intact endovascular endothelium, serotonin may interact with serotonin 1 receptors located on endothelial cells, indirectly resulting in local vasodilation by stimulating the local release of prostacyclin and nitric oxide. When endothelium is seriously dysfunctional, as it is assumed to be in severe early-onset preeclampsia,[21] the serotonin 1 receptor–mediated response may be diminished and serotonin is believed to react with serotonin 2 receptors on smooth muscle cells and platelets, resulting in direct vasoconstriction, amplifying the effects of other vasoconstrictors and augmenting effects on platelet aggregation and thrombus formation. These effects of serotonin on serotonin 2 receptors are selectively blocked by ketanserin, a serotonin 2 receptor blocker with some central and peripheral α_1-adrenoceptor antagonistic activity. Such side effects as somnolence, dizziness, and dryness of the mouth are sometimes reported during the initial days of treatment with ketanserin, and dose-dependent prolongation of corrected QT interval has been noted incidentally.

In this study fewer maternal complications developed and fewer side effects were noted with ketanserin than with dihydralazine. A recent study by Rossouw et al[22] comparing repeated intravenous bolus injections of ketanserin and dihydralazine showed adequate blood pressure control in both groups. They concluded that ketanserin appeared to be the safer drug, because blood pressure was decreased more gradually and no hypotension occurred. In another study intravenous ketanserin was shown to be effective in achieving satisfactory blood pressure control in patients with severe preeclampsia resistant to conventional vasodilatory medication, and most of these patients spontaneously reported that they felt better after the addition of ketanserin.[23] Ketanserin was significantly more effective than atenolol and α-methyldopa in the relief of clinical signs and symptoms of severe preeclampsia in a study by Voto et al.[24]

Magnesium sulfate administration and the use of corticosteroids for fetal indications may influence maternal outcome. In The Netherlands, as in several other countries (eg, Belgium, South Africa, Australia), magnesium sulfate is not given routinely but is administered only in case of clinical suspicion of imminent eclampsia. Because the rates of additional use of magnesium sulfate and steroid administration were comparable in the 2 groups, however, interference with the results appears to be negligible. Furthermore, at the time of the study it was hospital policy not to administer intramuscular steroids for fetal indications to patients with a platelet count $<50 \times 10^9$ cells/L for fear of intramuscular hematoma.

The indication to terminate pregnancy immediately when HELLP syndrome is diagnosed[4, 5] was debated by Visser and Wallenburg.[2] With respect to HELLP syndrome, in the dihydralazine group all patients with this condition at inclusion, none of whom received steroids, still had HELLP syndrome at delivery. A significant number of other patients in the dihydralazine group acquired HELLP syndrome at or shortly after delivery (n = 7). With ketanserin, complete reversal of HELLP syndrome occurred before delivery in 2 patients with HELLP syndrome at inclusion and in 1 patient who acquired the condition during treatment. Of the 2 patients with HELLP syndrome at inclusion, 1 received steroids; however, this therapy was provided only after the return to normal of the platelet count. Although corticosteroid administration may affect laboratory parameters in HELLP syndrome, interference with the data in this study appears to be negligible because among the 38 patients who received corticosteroids 19 were in each treatment group. Beneficial effects of ketanserin on HELLP syndrome, a rise in platelet count and a marked relief of epigastric pain, have also been noted by Spitz et al.[25] Complications associated with HELLP syndrome have been reported to include abruptio placentae, acute renal failure, pulmonary edema, hepatic hematoma, liver rupture, and ascites. In this study 1 dihydralazine-treated patient with HELLP syndrome had a major cerebral hemorrhage and abruptio placentae during the initial phase of stabilization, 4½ hours after admission, leading to both maternal and fetal deaths. One other patient, also receiving dihydralazine, whose pregnancy was complicated by both HELLP syndrome and abruptio placentae had an uneventful recovery. None of the 4 patients with pulmonary edema showed evidence of HELLP syndrome.

Fluid retention, possibly caused by capillary leakage, is an accepted side effect of dihydralazine administration and is clearly demonstrated by the fall in urinary output observed after initiation of dihydralazine therapy. Urinary output with ketanserin was significantly greater for ≥4 consecutive days, and none of the patients in the ketanserin-group acquired pulmonary edema post partum. In contrast, 4 patients with dihydralazine did acquire this complication, and 2 of them required artificial ventilation and another had an eclamptic seizure.

Most maternal complications developed during the postpartum period. Immediate emergency delivery by the cesarean route of patients in unstable condition does not result in a decreased incidence of these postpartum complications. Sibai et al[26] found that HELLP syndrome

was associated with serious maternal morbidity, especially when it occurred in the postpartum period. In another study it was demonstrated that when severe preeclampsia was complicated by pulmonary edema this happened post partum in 70% of all cases.[27] Because the high incidence of postpartum pulmonary edema is of concern, among the most important findings of the current study is that the risk of this complication appeared to be associated with the use of dihydralazine.

Immediate blood pressure control effects were comparable between ketanserin and dihydralazine, whereas side effects and maternal complications occurred significantly less frequently with ketanserin treatment. Because this study compared 2 antihypertensive drugs for efficacy and safety, the inclusion criterion was severe hypertension. Because preeclampsia is a multisystem disease associated with generalized endothelial dysfunction, however, the maternal complications encountered were those of a multisystem disorder that may be arrested by treatment but has hitherto been curable only through delivery. As far as effects on the pregnant women are concerned, ketanserin appears to be superior to dihydralazine in the management of severe preeclampsia. This superiority may be related to the fact that selective serotonin 2 blockers may have a beneficial impact on the disturbed platelet–endothelial cell interaction in severe preeclampsia, rather than acting only as nonselective vasodilators.

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