# The effect of serotonergic blockade in postpartum preeclamptic patients

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Thirty postpartum preeclamptic patients from the University of South Florida Obstetrical Service were enrolled in a placebo-controlled, randomized, double-blind study to test the effectiveness of ketanserin in lowering the blood pressure. An intravenous bolus of ketanserin resulted in a significant drop in the mean arterial blood pressure. The decrease in the blood pressure could be maintained by a continuous infusion of ketanserin. Hypertension returned after the medication was discontinued. These observations suggest that ketanserin, a selective blocker of type II serotonin receptors, may be effective in acutely reducing elevated postpartum blood pressure in preeclamptic patients, and that serotonin may play a role in the pathogenesis of preeclampsia, but not be important as a mediator in the severity of the disease. (Am J Obstet Gynecol 1985;153:130-4.)

**Key words:** Postpartum preeclampsia, hypertension, ketanserin, type II serotonin receptors

Preeclampsia, a syndrome which complicates pregnancy after the twentieth week of gestation, is characterized by hypertension, proteinuria, and edema.[1] The etiology of it remains unknown, but the main physiopathologic concept held today is that arteriolar vasoconstriction is responsible. The mediators of this vasoconstriction, however, are unknown.

Serotonin is widely distributed in nature being found in plants and animals. In humans, over 90% of the serotonin is found in enterochromaffin cells in the gastrointestinal tract.[2] Serotonin is released mainly by increased intraluminal pressure into the portal blood circulation, where it is carried by platelets in such a way that it is protected from enzymatic degradation and from being pharmacologically active. Experimental studies have shown that exogenously infused serotonin, as well as serotonin released from platelets,[3] can cause vasoconstriction, hypertension,[4] antidiuresis, and edema—a syndrome similar to preeclampsia. In order to evaluate a possible role of serotonin in the pathogenesis of preeclampsia, we studied the effects of a peripheral serotonin receptor blocker, ketanserin (Janssen Pharmaceutica, New Brunswick, New Jersey), in a group of postpartum women with preeclampsia.

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## Material and methods

Thirty postpartum preeclamptic patients from the University of South Florida Obstetrical Service at Tampa General Hospital were enrolled in the study. The following criteria were used. *Criteria for inclusion:* (1) Patients admitted to Tampa General Hospital with diagnosis of preeclampsia by standard criteria[1]; (2) volunteered for study and signed informed consent; (3) postpartum diastolic blood pressure 90 mm Hg or greater but less than 110 mm Hg. *Criteria for exclusion:* (1) Denial of informed consent; (2) use of oral antihypertensive agents; (3) unusual obstetric complication; (4) parenteral antihypertensive within 1 hour of initiation of the protocol; (5) patients who planned to breast-feed.

Written informed consent was obtained prior to the inclusion in this study, which was approved by the Institutional Review Board for Human Investigation. The placebo and the active experimental drug were packed identically and labeled as drug A or B, 10 mg (5 mg/ml). Neither the patient nor the investigator knew which drug was being used at any given time.

Upon admission to the labor and delivery suite, the patient gave a complete history and underwent a physical examination, and the severity of the preeclampsia was assessed according to the standard definition.[1] Prior to and at the conclusion of therapy, samples were obtained for the determination of a complete blood count with a differential, SMA-12, platelet count, and urinalysis.

**Treatment protocol.** Each patient received ketanserin and placebo in a double-blind crossover fashion. Drug A or B was used in a random sequence. The initial

**Table I.** Demographic and obstetric data

| | |
|---|---|
| Median age (yr) | 21.5 |
| Race (%) | |
| Black | 50 |
| White | 43.34 |
| Hispanic | 6.66 |
| Median weight (pounds) | 174.4 (range, 115-333) |
| Primigravid (%) | 73.3 |
| Multiparous (%) | 26.7 |
| Mean gestational age (wk) | 37.2 |
| Mode of delivery | |
| Vaginal | 18 (66.6%) |
| Cesarean section | 8 (33.3%) |
| Singleton pregnancy | 25 |
| Twin pregnancy | 1 |

**Table II.** Selected clinical and laboratory data

| | | *Mean* | *Range* |
|---|---|---|---|
| Blood pressure (torr) | | | |
| Systolic | | 149.6 | 140-191 |
| Diastolic | | 96.9 | 91-124 |
| Mean | | 114.5 | 110-147 |
| Uric acid (mg/dl) | | 5.47 | 3.5-8.8 |
| Platelet count ($\times 10^3/mm^3$) | | 261.5 | 162-427 |
| Severity | | | |
| Mild | 16 (53%) | | |
| Severe | 13 (43%) | | |
| Eclampsia | 1 (03%) | | |
| Proteinuria | | | |
| 0 − + | 16 (53%) | | |
| + + − + + + + | 14 (46%) | | |
| Edema | | | |
| 0-Trace | 18 (60%) | | |
| + − + + + + | 12 (40%) | | |

10 mg bolus intravenous push was followed by the monitoring of vital signs every 5 minutes. If there was no response within 10 minutes, a second bolus was given. If there was no response to the second bolus, and the diastolic blood pressure was >90 mm Hg, then the alternative drug was used in the same fashion after a 30-minute wash-off period of time. If there was response to the first or second bolus, then a continuous intravenous infusion of the same drug was begun at 4 mg/hr, with increments of 2 mg/hr every 10 minutes to a maximum of 12 mg/hr. All side effects were recorded.

**Statistical analysis.** All recorded parameters were entered into an IBM 3725 and analyzed by means of the SAS statistical package. Mean arterial pressures were derived from systolic and diastolic measurements. Changes in arterial pressure after ketanserin or placebo were analyzed by means of the paired Student's *t* test. Comparisons between groups were made by using the general linear models procedure. Alterations in arterial pressure were compared between ketanserin and placebo and between mild and severe pregnancy-induced hypertension.

In addition to recorded parameters, a calculated placebo-adjusted response (the change after ketanserin less the change after placebo) was entered into analysis. All results were considered to be significant at the $p < 0.05$ level.

## Results

Table I presents the demographic and obstetric data. The median age was 21.5 years (range, 13 to 31 years). Fifty percent of the patients were black, 43.34% were white, and 6.66% were Hispanic. The median antepartum weight was 174.4 pounds (range, 115 to 333 pounds).

The mean gestational age was 37.2 weeks. Most of the patients were primigravid (73.3%), with a singleton pregnancy (96.7%), and most were delivered vaginally (66.6%). Table II presents selected clinical and laboratory features of preeclampsia for this study population.

Three patients developed hypotension, and one patient developed tachycardia with hypotension shortly after the first infusion was begun. These four patients did not receive the second infusion. Three additional patients did not fulfill all the criteria for the study. Thus, seven patients were excluded from analysis. Another patient complained of a generalized burning sensation during the intravenous infusion of the bolus of ketanserin. The effect lasted for 10 minutes and the patient continued on the treatment protocol without further side effects.

An intravenous bolus of ketanserin resulted in a significant drop in the systolic, diastolic, and mean arterial pressures. There also appeared to be some decrease in mean arterial pressure after infusion of placebo. Regression analysis of the response demonstrated, however, that the response to ketanserin was significantly greater than the response to placebo ($p < 0.01$) (Fig. 1).

In an attempt to evaluate the role of serotonin in the severity of preeclampsia, patients were grouped according to severity. The change in mean arterial pressure after infusion of ketanserin in patients with mild or severe preeclampsia may be seen in Fig. 2. There was no statistical difference in response between these groups. Although measurements of mean arterial pressure after infusion of placebo appeared to demonstrate a greater reduction in blood pressure in patients with severe preeclampsia than in those with mild preeclampsia, there was wide variation and this trend did not achieve statistical significance (Fig. 3). The importance of the difference of the placebo effect between groups was more apparent when the placebo-adjusted re-

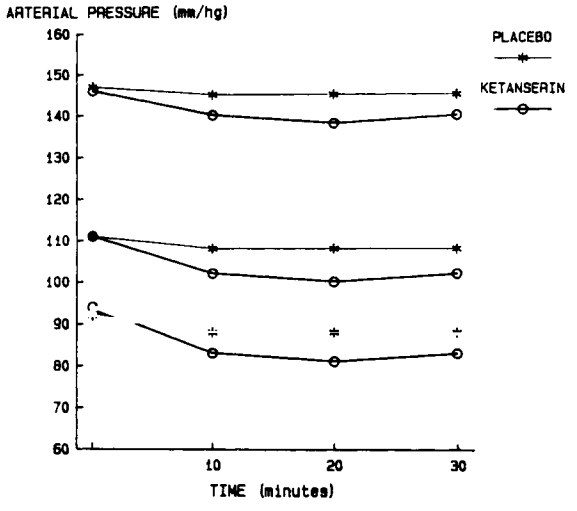


**Fig. 1.** Systolic, diastolic, and mean arterial blood pressures in postpartum patients with preeclampsia in response to injection of placebo or ketanserin; n = 23, differences between groups, F = 9.66, $p < 0.01$.

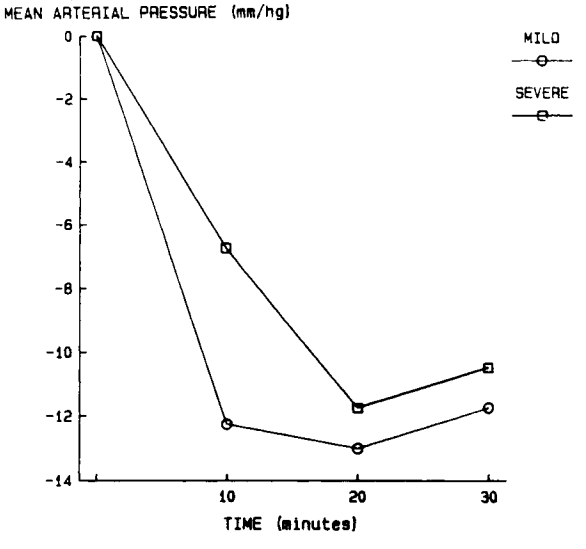


**Fig. 2.** Changes in arterial pressure in response to ketanserin in postpartum women with mild (n = 15) and severe (n = 8) preeclampsia; differences between groups, F = 1.38, $p > 0.05$.

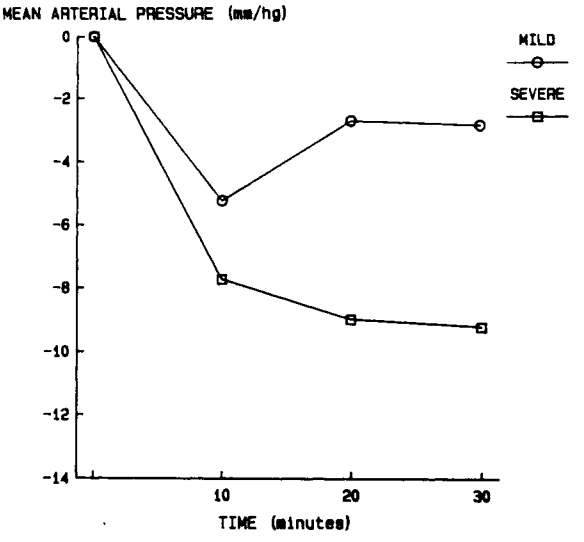


**Fig. 3.** Change in mean arterial pressure in response to placebo in postpartum patients with preeclampsia grouped according to severity; differences between groups, F = 1.57, $p > 0.05$.

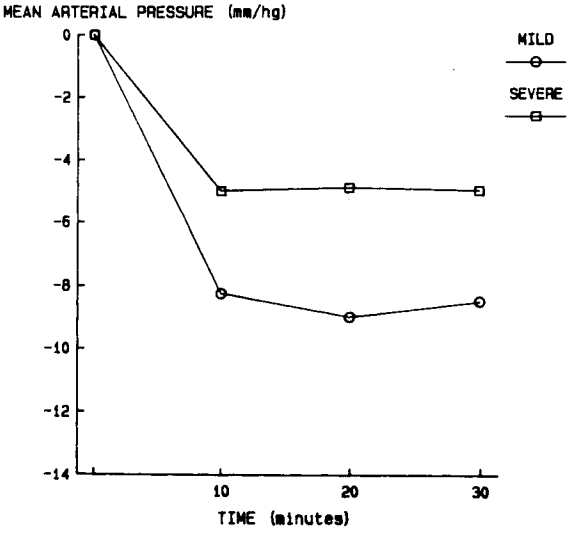


**Fig. 4.** Placebo-adjusted change in mean arterial pressure in response to ketanserin in preeclamptic patients grouped according to severity; differences between groups, F = 4.70, $p < 0.05$.

sponse to ketanserin was calculated (Fig. 4). These results demonstrate a significantly greater placebo-adjusted reduction in mean arterial pressure in response to ketanserin in mild preeclampsia.

## Comment

Ketanserin is a quinazoline derivative. The major mode of action involves antagonism of vasoconstriction due to serotonin type II receptor blockade and possibly an additional blocking effect on $\alpha_1$ and $\alpha_2$ adrenergic receptors.[5, 6] At high-dose levels, it exerts a depressant activity on the central nervous system. Thus far, ketanserin has demonstrated no teratogenic, mutagenic, or carcinogenic potential.[7, 8]

The suggestion has been made that serotonin plays a role in the pathogenesis of preeclampsia, but the results reported in the literature are conflicting. Some workers, but not all, have found increased blood levels of serotonin in preeclampsia.[9-11]

Serotonin is released during platelet aggregation at the time of intervillous hemorrhage.[10] Under this circumstance, serotonin becomes pharmacologically active. On the other hand, it has been shown that placentas from patients with preeclampsia have a de-

creased concentration of monoamine oxidase,[12] which increases the availability of catecholamine and serotonin because of its decreased metabolism. Additionally, it has been established that serotonin amplifies the vasoconstriction and platelet aggregatory effects of other agents, such as norepinephrine, angiotensin, and prostaglandins.[13] It is tempting to postulate that the cycle of continuous production of serotonin is then established and is stopped only when the placenta is delivered.

Parenteral administration of serotonin produced hypertension as a result of vasoconstriction. Ketanserin blocks this response in experimental animals and prevents hypertension in response to endogenous secretion of serotonin in patients with carcinoid syndrome.[14] When given to healthy volunteers, no significant change in the blood pressure and cardiac output is noted.[15] In subjects with essential hypertension, the administration of ketanserin is associated with a fall in blood pressure.[16] This response is thought to be secondary to a blockade of $\alpha_1$ as well as serotonergic receptors. In a study of women with hypertension secondary to preeclampsia, Weiner et al.[17] demonstrated a significant reduction in blood pressure in response to the administration of ketanserin.

The objective of this study was to examine the effects of ketanserin in lowering the blood pressure in the postpartum period of preeclamptic patients. At the doses used in this study, ketanserin produced a significant fall in arterial blood pressure in postpartum patients with preeclampsia, thus indicating a possible role of serotonin in this disease. The role of serotonin in the severity of arterial hypertension, however, was more difficult to demonstrate, since the spontaneous decrease in mean arterial pressure after delivery appeared to be greater in patients with severe preeclampsia. When this effect was compensated for, it was demonstrated that those patients with postpartum severe preeclampsia were less responsive to ketanserin. The results therefore provide indirect evidence that serotonin is not important as a mediator in the severity of the disease.

In summary, these studies indicate that serotonin may play a role in the pathogenesis of mild preeclampsia, but that the severity of arterial hypertension is mediated by other mechanisms.

## REFERENCES

1. Pritchard JA, MacDonald PC. Williams obstetrics. 16th ed. New York: Appleton-Century Crofts, 1980:665-700.
2. Thompson JH. Serotonin and the alimentary tract. Res Commun Chem Pathol Pharmacol 1971;2:687-781.
3. Zucker MB. The platelet release reactions. In: Hirsch J, Cade JF, Gallus AS, Schonbaum E, eds. Platelets, drugs and thrombosis. Basel: Karger S, 1975:27-34.
4. Blackshear JL, Orlandi C, Garnic JD, Hollenberg NK. Serotonin induces large artery spasm in vivo via $5HT_2$ receptors. Circulation 1983;68:197.
5. Kalkman HO, Pieter BM, Timmermans PB, Van Zwieten PA. Characterization of the antihypertensive properties of ketanserin (R41468) in rats. J Pharmacol Exp Ther 1982;222:227-31.
6. Rion R, Mena MA, Hong E. On the mechanism of action of ketanserin, a selective antagonist of the $S_2$ receptors with antihypertensive activity. Proc West Pharmacol Soc 1983;26:373-5.
7. Janssen Pharmaceutica dominant lethal test in female mice. Janssen Pharmaceutica Toxicological Research Report no. 897. August, 1979.
8. Janssen Pharmaceutica. Embryotoxicity and teratogenicity study in Wistar rats (segment III). Janssen Pharmaceutica Toxicological Research Report no. 891. July, 1979.
9. Carter BF, Cherry WB, Crenshaw C. Serotonin studies in abnormal pregnancies. AM J OBSTET GYNECOL 1967; 84:913-8.
10. Ramadan MA, Sammour M, Ibrahim F, et al. Serotonin (5-hydroxytryptamine) concentration in blood and placenta of normal and pre-eclamptic patients. Int J Biochem 1973;4:111-5.
11. Telen I, Fananapazir L, Crawford TBB. The possible relation between late pregnancy hypertension and 5-hydroxytryptamine levels in maternal blood. Br J Obstet Gynaecol 1979;86:468-71.
12. De Maria JF. Placental monoamine oxidase in normal and toxemic patients. AM J OBSTET GYNECOL 1964;88:490-4.
13. De Clerck F, David JL, Janssen P. Serotonergic amplification mechanisms in blood platelets. In: De Clerck F, Vanhoutte PM, eds. 5-Hydroxytryptamine in peripheral reactions. New York: Raven Press, 1982;83-94.
14. Bennier JJ, Blum AL. R41468 in the treatment of carcinoid syndrome. Janssen Pharmaceutica Pre-clinical Research Report no. 6. September, 1979.
15. Scheijgrond HW. Effect on blood pressure of oral doses of 10, 20, and 40 mgs R41468 in healthy volunteers. Clinical Research Report on R41468 no. 24. September, 1980.
16. Reimann IW, Frolich JC. Mechanism of hypertensive action on ketanserin in man. Br Med J 1983;287:391-3.
17. Weiner CP, Socol MD, Vaisrub N. Control of preeclamptic hypertension by ketanserin, a new serotonin receptor antagonist. AM J OBSTET GYNECOL 1984;149:496-500.

*Editors' note.* This manuscript was revised after these discussions were presented

## Discussion

**DR. DONALD M. SHERLINE,** Augusta, Georgia (By invitation). As natural body compounds go, serotonin or 5-hydroxytryptamine has a relatively short history. Rapport et al.[1] first isolated serotonin in 1948, and characterized it as the "vasoconstrictor substance in beef serum." Within only 3 years it was synthesized.[2] Then a long series of conflicting experiments on different species of animals was carried out in an effort to clarify the actions of this compound. Most of us became familiar with serotonin through its action in carcinoid syndrome and associated it with the flushing, hypertension, and diarrhea seen in that syndrome. Its presence has also been felt in neurology, psychiatry, genetics, gastroenterology, cardiology, and now in obstetrics through its association with hypertension and preeclampsia.

The authors cited previous studies demonstrating increased levels of serotonin in preeclampsia and used that, plus animal studies demonstrating hypertension,