specific for commercially prepared soy bean antigens (74,4%) and the soy bean extracts that were prepared from the soy bean dust collected on site (84,9%).[11] This shows that although cross-reactivity did occur there were differences between the commercial soy bean extracts and the extracts prepared from dust collected on site. There may be differences in the antigenic components of soy bean species from different countries, and locally manufactured RAST tests may be required. Variability in the allergen content of soy bean SPT samples could result from the methods used to prepare the extracts, selection of raw material, storage conditions, standardisation, quality and potency of extracts.[12] Human error and the interpretation of SPTs could also account for variability of results.

The poor association between tests of sensitisation and disease may be explained by factors associated with the subjects themselves. High levels of soy bean dust in the workplace are likely to produce symptoms caused by nonspecific irritation, in which case measures of specific IgE will clearly be inappropriate. The questionnaire as a measure of disease outcome is problematic when not supported by more objective methods. For example, workers may hide symptoms to protect jobs if diagnosis of a work-related condition may lead to dismissal. Tests for sensitisation may be associated with particular symptom complexes and disease, rather than with nonspecific symptoms consistent with allergic disease. A more targeted approach may thus be indicated.

Conclusion

In this study soy bean-specific IgE tests failed to identify workers with symptoms consistent with allergic disease. This does not necessarily mean that these tests are not useful, as many remedial factors may explain the disappointing results. The tests were associated with exposure, however, an important factor given that exposure may be denied or unknown.

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Ketanserin and hydralazine in hypertension in pregnancy — a randomised double-blind trial

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Objectives. To compare ketanserin with hydralazine in the treatment of hypertension in late pregnancy.

Study design. Randomised control trial. Ten milligrams ketanserin were compared with 5 mg hydralazine, both given intravenously to 10 patients in each group. Blood pressure, maternal and fetal heart rate and umbilical and arcuate artery Doppler flow velocimetry waveforms were recorded before and every 10 minutes after administration of the drug.

Results. No significant differences were found between the two drugs in respect of initial blood pressures and readings taken 10 minutes after each 30-minute administration. One patient in the hydralazine group developed severe hypotension and fetal distress for which a caesarean section was performed. No change in the flow velocity waveforms of umbilical and arcuate arteries was noticed.

Conclusion. No unforeseen complications followed the administration of ketanserin. No major differences in the effects of the two drugs could be detected. Ketanserin appears to be safer as no hypotension occurred, and it reduced blood pressure more gradually. As ketanserin could become an alternative to hydralazine, more studies with larger numbers of patients are needed to compare it with hydralazine.

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Hypertension complicates 7 - 10% of pregnancies and is associated with high maternal and fetal morbidity and mortality.[1,2] The most frequent cause of maternal mortality in pre-eclampsia is cerebral haemorrhage.[3] Antihypertensive therapy can prevent this severe complication and can help postpone delivery for 48 hours during which time steroids can improve lung maturity in preterm infants.[4]

Hydralazine, a vasodilator, is at present most frequently used in hypertensive crises during pregnancy.[5] Its use however, has disadvantages and side-effects, namely

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hypotensive episodes with fetal distress, variation in peak effect, headaches, tachycardia, SLE-like syndrome and tachyphylaxis.[6-8] There is therefore a need for new drugs with fewer side-effects. The serotonin antagonist ketanserin is a possibility.

Type 2-serotonin receptors are present on platelets and the smooth muscle of blood vessels.[9] Serotonin aggregates platelets and augments the vasoconstrictor response to angiotensin II, histamine and catecholamines. Aggregation of platelets releases serotonin into the serum.[10] As patients with pre-eclampsia are more sensitive to the pressure response to angiotensin II and have lowered platelet counts[11,12] it can thus be postulated that serotonin plays a role in the pathophysiology of pre-eclampsia.

Ketanserin is a 5-hydroxytryptamine type 2-receptor antagonist with 21-adrenoreceptor activity, and selectively blocks these receptors.[13] Studies have shown that ketanserin effectively lowers blood pressure in puerperal and pregnant patients and in a patient with pre-eclampsia where intra-uterine death had occurred.[9,14,15] However, there are no studies to demonstrate its effect on uteroplacental vascular resistance. Before large randomised controlled trials are undertaken, in-depth studies are needed to exclude possible harmful changes in uteroplacental vessels.

A double-blind randomised control trial was therefore undertaken to compare the antihypertensive effects of hydralazine and ketanserin and to study their effects on fetal heart rate and especially on umbilical and arcuate artery flow velocity waveforms.

Patients and methods

Patients who are more than 28 weeks pregnant and have a diastolic blood pressure more than 110 mmHg after 5 minutes' rest, or 100 mmHg or more on two occasions at least 30 minutes apart, were selected for the study. Patients with the following conditions were excluded: fetal distress, antihypertensive treatment during the preceding 12 hours and epidural anaesthesia. Magnesium sulphate therapy was not regarded as a contraindication for inclusion in the study.

A Doppler 9000 continuous wave machine with a 4 MHz transducer and 200 Hz filter was used to measure the flow-velocity waveforms of the umbilical artery. A mean of 5 consecutive waveforms was used to calculate the resistance index (RI). Measurements were only made when the umbilical vein waveform was also visible and while the fetus was still and not breathing. Arcuate artery flow velocity measurements were done in a similar way. All measurements in a specific patient were taken on the same side. Two measurements were taken to calculate a mean RI before the drugs were given. After the drug administration, measurements were repeated every 10 minutes at the same level. Each patient received 80 ml/h of a balanced electrolyte solution (Plasmalyte B from Sabax) intravenously. After informed consent had been obtained, patients were randomised by means of sealed envelopes to receive either ketanserin or hydralazine. A person not involved in the clinical management of the patient prepared the drugs for injection. In the case of hydralazine the syringe was filled with a 2 ml solution containing 5 mg of the drug. In the case of ketanserin the syringe contained 10 mg of the drug, also in a 2 ml solution. Therefore, it was impossible for the clinician to know which drug was being used. The drug was slowly administered intravenously over 2 minutes and repeated after 20 minutes if the desired reduction of diastolic blood pressure to below 100 mmHg had not been obtained.

Ten patients received either ketanserin or hydralazine. Doppler results were available in 18 patients of whom 9 received hydralazine and 9 received ketanserin. Four of the ketanserin group and 6 of the hydralazine group received magnesium sulphate of which 4 g were given intravenously and 10 g intramuscularly as a loading dose and thereafter 5 g intramuscularly every 4 hours. Each of the patients receiving hydralazine received only one dose (5 mg) to reach the therapeutic goal, while 6 of the patients receiving ketanserin needed 10 mg, 3 patients needed 20 mg and 1 patient needed 30 mg to reach the therapeutic goal.

As some of the patients needed more than one dose of ketanserin to reach the therapeutic goal, results obtained before administration of the agents and during the first 30 minutes thereafter were used to compare the two groups of patients. The effects of ketanserin and hydralazine were firstly assessed separately in each group, after which the two groups were compared with each other in respect of systolic and diastolic blood pressure and maternal pulse and fetal heart rate.

Student's *t*-test was used to compare maternal age, gravidity, birth weight and duration of pregnancy. The one-way analysis of variance (ANOVA) was used to evaluate the effect of the two drugs on mean systolic and diastolic blood pressure, pulse rate and fetal heart rate. To compare the frequency of proteinuria in the two groups, Fisher's exact test was used. A P-value < 0,05 was significant. The study was approved by the Tygerberg Hospital Ethics Committee.

Results

The two groups of patients were comparable in respect of age, gravidity, duration of pregnancy and body mass (Table I). Proteinuria was present in 9 of the 10 patients who received ketanserin as well as in 8 of the 10 who received hydralazine. Severe proteinuria (3+ or more on dipstick testing) was present in 4 of the patients who received hydralazine. No patient in the ketanserin group had severe proteinuria. This difference was significant (Fisher's exact test, $P < 0,05$).

Table I. Comparison of patients who received either ketanserin or hydralazine (mean values and ranges)

	Ketanserin	Hydralazine	*P*-value
Age (yrs)	24 (15 - 36)	26,6 (15 - 40)	0,54
Gravidity	2 (1 - 6)	2 (1 - 4)	0,59
Birth weight (g)	2 465 (1 040 - 3 680)	2 329 (1 040 - 3 640)	0,55
Pregnancy duration (wks)	37,1 (31 - 41)	35,6 (30 - 39)	0,27

The mean systolic blood pressure in the ketanserin group of patients was 147 mmHg before administration of ketanserin, 142 mmHg after 10 minutes, 138 mmHg after 20

minutes and 130 mmHg after 30 minutes. It was not significantly lowered in the first 30 minutes by ketanserin ($P = 0,34$). Hydralazine lowered the systolic blood pressure significantly ($P < 0,001$) with a pretreatment mean reading of 155 mmHg, 140 mmHg 10 minutes after the drug had been given, 135 mmHg after 20 minutes and 137 mmHg after 30 minutes. There was no statistical difference in the systolic antihypertensive effect of ketanserin and hydralazine at 10, 20 and 30 minutes when compared to each other (Table II).

Table II. Median values and ranges of systolic blood pressure (mmHg) before and after administration of antihypertensive drugs, and the changes over 30 minutes

	Ketanserin	Hydralazine	*P*-value
Before admin.	147 (140 - 210)	155 (145 - 180)	0,14
After 10 min	142 (120 - 200)	140 (120 - 160)	0,24
After 20 min	138 (110 - 190)	135 (110 - 150)	0,17
After 30 min	130 (110 - 190)	137 (100 - 145)	0,14

The mean diastolic blood pressure before administration of ketanserin was 110 mmHg, 100 mmHg after 10 minutes, 95 mmHg after 20 minutes and 90 mmHg after 30 minutes. This lowering of diastolic blood pressure in the ketanserin group was significant ($P = 0,001$). The corresponding blood pressure in the hydralazine group was 110 mmHg before administration, 95 mmHg after 10 minutes and 90 mmHg after 20 minutes. This reduction in diastolic blood pressure was also significant ($P < 0,001$). When compared to each other there was no difference in the diastolic effect over 10, 20 and 30 minutes (Table III).

Table III. Median values and ranges of diastolic blood pressure (mmHg) before and after administration of the antihypertensive drugs

	Ketanserin	Hydralazine	*P*-value
Before admin.	110 (110 - 120)	110 (105 - 125)	0,14
After 10 min	100 (80 - 113)	95 (85 - 110)	0,74
After 20 min	95 (80 - 110)	90 (80 - 95)	0,09
After 30 min	90 (85 - 110)	90 (60 - 95)	0,14

Although hydralazine had a tendency to cause maternal tachycardia, neither agent had a statistically significant influence on maternal pulse rate or fetal heart rate (Tables IV and V).

Table IV. Median values and ranges of maternal pulse rate (/min) before and after administration of the antihypertensive drugs

	Ketanserin	Hydralazine	*P*-value
Before admin.	82 (64 - 96)	82 (72 - 100)	0,14
After 10 min	80 (72 - 104)	90 (64 - 104)	0,81
After 20 min	80 (96 - 108)	88 (76 - 112)	0,15
After 30 min	84 (64 - 108)	94 (60 - 120)	0,21

Table V. Mean values and ranges of the fetal heart rate (/min) before and after administration of the antihypertensive drugs

	Ketanserin	Hydralazine	*P*-value
Before admin.	143 (128 - 178)	138 (125 - 146)	0,73
After 10 min	144 (126 - 180)	136 (128 - 158)	0,70
After 20 min	144 (120 - 176)	139 (120 - 150)	0,75
After 30 min	146 (135 - 180)	137 (60 - 148)	0,07

There were no abnormal-velocity waveforms found with either agent in any of the patients. (Values exceeding 95th percentile line of curves determined for the Western Cape population were considered abnormal.[16]) Neither drug caused any change in flow-velocity waveforms of the umbilical or arcuate arteries (Tables VI and VII).

Table VI. RI values of the umbilical artery (mean and SD)

	Ketanserin	Hydralazine
Before admin.	0,65 (0,12)	0,62 (0,07)
After 10 min	0,63 (0,14)	0,64 (0,08)
After 20 min	0,66 (0,14)	0,63 (0,09)
After 30 min	0,66 (0,12)	0,63 (0,03)

Table VII. RI values of the arcuate artery (mean and SD)

	Ketanserin	Hydralazine
Before admin.	0,44 (0,11)	0,51 (0,10)
After 10 min	0,45 (0,11)	0,52 (0,12)
After 20 min	0,45 (0,15)	0,56 (0,08)
After 30 min	0,46 (0,11)	0,53 (0,11)

The only complication directly related to ketanserin was dizziness, which occurred in 1 patient 10 minutes after administration. It cleared spontaneously after 15 minutes. In contrast, 1 patient in the hydralazine group who was 30 weeks pregnant developed severe complications of acute hypotension, namely convulsions and severe fetal distress, 30 minutes after administration of the agent. After resuscitation, a live infant of 1 040 g was delivered by caesarean section. Another patient experienced tachycardia of 120/min and a headache 30 minutes after administration of hydralazine. Although probably not directly related to the use of hydralazine, 2 patients developed an abruption of the placenta 5 and 6 hours respectively after the study had been completed. One of these fetuses died. One of the 10 patients receiving ketanserin was delivered by caesarean section. This particular patient, 31 weeks pregnant, developed eclampsia 2 days after completion of the study. The fetus weighed 1 040 g and did well neonatally. There were 5 caesarean sections in the hydralazine group. The indications for these were an increase in the severity of pre-eclampsia, fetal distress (due to hypotension), failed induction, poor progress during labour, and abruptio placentae.

Discussion

The high maternal mortality rate associated with severe pre-eclampsia and eclampsia necessitates the use of antihypertensive drugs in these patients.[1,2] As parenteral administration of hydralazine is often complicated by late decelerations of the fetal heart rate, especially in the growth-retarded fetus, there is a need for the use of safer drugs. A sudden and substantial decline in maternal blood pressure in the case of placental insufficiency is particularly undesirable. Previous experience with ketanserin demonstrated that a sudden fall in blood pressure was unlikely.[9,15] This was again confirmed in this study where the systolic blood pressure did not fall below 110 mmHg or the

diastolic blood pressure below 85 mmHg. In contrast, the lowest systolic and diastolic blood pressures recorded in the hydralazine group were 100 and 60 mmHg respectively. Although ketanserin administration did not significantly lower the systolic blood pressure in the first 30 minutes, this could have been a result of the small numbers as the mean systolic blood pressure in effect declined from 147 mmHg to 130 mmHg. As the second administration was effective in lowering the blood pressure further, it probably reflects the safe and gradual effect of ketanserin. It should, however, be remembered that the patients in the hydralazine group could have had more severe pre-eclampsia, as reflected in the higher initial blood pressure (although not significantly so) and more severe proteinuria.

As no changes in the Doppler flow-velocity waveforms were observed, a sudden alteration in the placental or uterine resistance was excluded. However, as flow-velocity waveforms do not give an indication of blood flow, one cannot make too many conclusions from the constant flow-velocity patterns. As no patient demonstrated absent end-diastolic flow, the study did not reflect patients with high placental resistance and thus intra-uterine growth retardation; one cannot therefore make too many conclusions from the small effect on the flow-velocity waveforms. Because a several-fold increase in placental resistance due to umbilical artery constriction is necessary to influence the flow-velocity waveforms, minor changes will not be noted.[17] Although the greater number of caesarean sections in the hydralazine group can certainly not be attributed to this drug, this finding as well as the uncontrolled fall in blood pressure raise some questions regarding its safety. This is further supported by the findings of Vinck *et al.* that the fetus was growth-retarded in 92,8% of instances when late decelerations occurred after antihypertensive therapy.[18,19] On the other hand, patients in the hydralazine group had more severe pre-eclampsia and the greater number of caesarean sections in this group could have occurred by chance.

This study has shown that the administration of ketanserin during labour is free of severe adverse effects, but was too small to demonstrate advantages over hydralazine. As ketanserin has the potential to be an alternative drug to hydralazine, more randomised control trials are needed to compare them.

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50 years ago . . .

The ideal condition would be for Government laboratories to manufacture drugs and control their distribution and sale through Government dispensaries, health centres and pharmacies. Until such time as this can be achieved, the following recommendations are suggested:

1. A Government department (Food, Drugs and Cosmetics) with inspectors to be charged with the duty of enforcing these recommendations.
2. Prohibition of secret remedies.
3. Proprietary medicines to be registered and to have disclosed on advertisements and labels clearly and distinctly full qualitative and quantitative details of the constituents.
4. Prohibition in medical advertisements and on labels of preparations of names of diseases recommended for treatment . . .
5. Prohibition of false and misleading advertisements and illustrations.
6. Price control, as during war-time. Vitamins to be made available at low cost.

Further steps to be taken:

7. Education of young and old regarding what should not be done and what can be done in the event of illness. Government health centres would help in this regard.
8. Establishment of adequate medical services within easy reach of every member of the population.

(N. Sapeika, *S A Medical Journal*, 23 June 1945, p 202).