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%). 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. 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.

We thank the factory management for access to the factory, the workers for their co-operation and Ruth Mkwele-Radebe and Kate Hlaza for administering the questionnaires.

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

H. J. Rossouw, G. Howarth, H. J. Ondendaal

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.


Hypertension complicates 7 - 10% of pregnancies and is associated with high maternal and fetal morbidity and mortality. Antihypertensive therapy can prevent this severe complication and can help postponation of delivery for 48 hours during which time steroids can improve lung maturity in preterm infants. Hydralazine, a vasodilator, is at present most frequently used in hypertensive crises during pregnancy. Its use however, has disadvantages and side-effects, namely...
hypotensive episodes with fetal distress, variation in peak effect, headaches, tachycardia, SLE-like syndrome and tachyphylaxis. 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. Serotonin aggregates platelets and augments the vasoconstrictor response to angiotensin II, histamine and catecholamines. Aggregation of platelets releases serotonin into the serum. As patients with pre-eclampsia are more sensitive to the pressure response to angiotensin II and have lowered platelet counts, 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. 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. However, there are no studies to demonstrate its effect on utero-placental vascular resistance. Before large randomised controlled trials are undertaken, in-depth studies are needed to exclude possible harmful changes in utero-placental 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)

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

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
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. 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. 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.6,7 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, 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.

We wish to thank the Chief Medical Superintendent of Tygerberg Hospital, Dr. G. A. Schoombee, for permission to publish. This study was supported by the Medical Research Council.

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Accepted 15 Nov 1993.

The South African Medical Journal.

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.
8. Establishment of adequate medical services within easy reach of every member of the population.