GUANFACINE IN THE TREATMENT OF HYPERTENSION DUE TO PRE-ECLAMPTIC TOXAEMIA IN THIRTY WOMEN

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- 1 Thirty pregnant women aged 22–34 yr presenting with pre-eclampsia were treated with guanfacine for periods of 16–68 days.
- 2 Elevated blood pressure was lowered to a statistically and clinically significantly extent in the first week of treatment, falling almost to normal levels before parturition in 24 cases. Four days after delivery all the patients had normal blood pressures.
- 3 Oedema (localized or generalized) was not reduced to any extent by guanfacine and additional treatment was necessary in 17 cases. There was little effect on proteinuria.
- 4 Twenty-five patients reported side-effects attributable to the treatment (sedation in 25 cases, dryness of the mouth in 15, and feelings of dizziness in 6 cases).
- 5 No notable changes were observed in either foetal or maternal heart rate during the period of treatment. Of the 30 deliveries, 19 were spontaneous, 5 by vacuum extraction, and 6 were by Caesarean section because of suspected placental insufficiency. Six of the infants were 'small-for-date babies', but all developed normally later.

Methods

BETWEEN March 1977 and February 1978, 30 pregnant women aged 22–34 yr suffering from pre-eclampsia were treated with guanfacine at Kiel University Women's Hospital. The purpose of the trial was explained to the patients, who gave their consent to participate. Ten were nulliparae, twelve were primiparae and eight multiparae. The purpose of the trial was to determine whether the use of guanfacine would reduce the incidence of surgical delivery and/or neonatal morbidity. In addition observations were made regarding the efficacy and safety of the drug and its interaction with other medication affecting the principal obstetric parameters. The total observation period comprised an antepartum phase of maximum 10, minimum 4 weeks, the period of delivery and hospital confinement (1–2 weeks), and a follow-up phase of 2–8 weeks' duration after the patient's discharge from hospital. The whole period of observation thus ranged from 14–20 weeks, during which time the relevant data were recorded at the following stages: (a) baseline data at entry into trial; (b) checks at intervals until delivery; (c) observations on the course of labour and examination of infant; (d) observations on the course of the postpartum period and checks following discharge and observations on the early development of infant.

Guanfacine was given in the form of tablets of

1 mg, the starting dose being 1 tablet twice daily. This was later increased on an individual basis up to a maximum of 6 mg daily.

The following clinical information and history were recorded: age at menarche, regularity of menstruation, number of previous deliveries and abortions, time of last menses, probable date of delivery, measurement of circumference of abdomen, pelvimetry, foetal heart rate, symptoms of pre-eclampsia (oedema, proteinuria, hypertension), cervical score, amnioscopy, ultrasound, documentation of the course of delivery including all the usual obstetric parameters, morphological examination of the placenta, and the recording of clinical and laboratory variables postpartum.

Initially the clinical variables were assessed at weekly intervals, then later more frequently. In addition each patient's age, height, weight and blood group were recorded as well as details of any additional treatment required and any side-effects observed. At each check-up the following laboratory tests were performed: complete blood picture, urea, creatinine, SGOT, SGPT, alkaline phosphatase, bilirubin, electrolytes, and complete urine analysis.

Before discharge the patients were given a final clinical and laboratory assessment by the investigator.

Results

Antenatal checks

As the patients entered the trial at different times, the duration of treatment varied. For this reason only the following values of the principal variables (blood pressure (mm Hg) pulse rate (beats/min), foetal heart rate (beats/min), weight (kg), circumference of abdomen (cm)) were subjected to statistical analysis, using Wilcoxon's test for differences between pairs of observations (significance level $2\alpha = 0.05$): mean value at examination No. 1 (entry into the trial) compared with values 2 and 3 (mean values for weekly check-ups between entry and parturition) and value 10 (last check-up before parturition). Average blood pressure values (systolic and diastolic/lying, and standing) and heart rates (lying and standing) plus s.d. and degrees of significance for the times mentioned are shown in Table 1.

Decreases in both systolic and diastolic blood pressures occurred between entry and parturition, which were both statistically highly significant and clinically relevant (supine systolic blood pressure decreased from 159 to 135 mm Hg, standing systolic blood pressure from 164 to 138 mm Hg, supine diastolic blood pressure from 104 to 88 mm Hg, and standing diastolic blood pressure from 106 to 92 mm Hg).

Mean heart rate reductions, on the other hand, though statistically significant, were not clinically relevant (supine from 71 to 69 beats/min and standing from 75 to 72 beats/min).

An even clearer picture of the efficacy of the treatment emerges if we ascertain the number of patients each week with normalized blood pressure (<140/98 mm Hg in the lying position) (Table 2). Only in six cases was blood pressure still raised slightly at the last check before labour began.

Table 2 The number of patients each week with normalized blood pressure after starting treatment with guanfacine

	First week after entry	Second week after entry	Final pre- partial check
No. of patients with normal blood pressure	18	21	24
Percentage	60	70	80

Mean values and significance levels for the variables weight, abdominal circumference and foetal heart rate are shown in Table 3. The increases in body weight and abdominal circumference were both highly significant and clinically relevant (mean body weight from 75 to 78 kg, mean circumference from 89 to 96 cm), but there was no significant change in foetal heart rate.

Table 1 Mean blood pressure (supine and standing, systolic and diastolic) and pulse rate (supine and standing) values in the antepartum period

Variable	Check 1	Check 2	Check 3	Check 10
<i>Supine blood pressure (mm Hg)</i>				
Systolic	159.67	140.33	136.00	135.50
s.d.	± 8.90	± 9.91	± 5.48	± 5.92
Significance	—	***	***	***
Diastolic	104.83	93.50	90.33	88.00
s.d.	± 7.48	± 10.60	± 8.19	± 7.50
Significance	—	***	***	***
<i>Standing blood pressure (mm Hg)</i>				
Systolic	164.33	142.33	139.67	138.60
s.d.	± 9.35	± 8.98	± 6.01	± 4.76
Significance	—	***	***	***
Diastolic	106.33	94.83	93.67	92.33
s.d.	± 6.15	± 9.14	± 6.81	± 7.28
Significance	—	***	***	***
<i>Pulse rate (beats/min)</i>				
Supine	71.87	69.53	69.20	69.53
s.d.	± 4.70	± 3.14	± 3.35	± 4.35
Significance	—	*	**	*
Standing	75.67	72.53	72.33	72.87
s.d.	± 4.93	± 3.44	± 3.57	± 4.22
Significance	—	**	**	*

* $2 P < 0.05$; ** $2 P < 0.01$; *** $2 P < 0.001$

Check 1 = value at entry into trial; checks 2 and 3 = values at weekly antenatal checks; check 10 = value at last check before parturition.

Table 3 Mean body weight, abdominal circumference and foetal heart rate in the antepartum period ($n = 30$)

Variable	Check 1	Check 2	Check 3	Check 10	Check 11
Weight (kg)	75.48	76.02	76.82	78.05	—
s.d.	± 7.56	± 7.40	± 7.63	± 7.63	—
Significance	—	***	***	***	—
Abdominal circumference (cm)	89.00	90.40	91.93	96.47	—
s.d.	± 6.70	± 6.40	± 6.51	± 5.53	—
Significance	—	***	**	***	—
Foetal heart rate (beats/min)	144.73	143.30	142.20	144.27	143.10
s.d.	± 7.10	± 7.84	± 6.97	± 9.78	± 11.67
Significance	—	NS	NS	NS	NS

*** 2 $P < 0.001$; NS, not significant.

Check 1 = value at entry into trial; checks 2 and 3 = values at weekly antenatal check; check 10 = value at last check before parturition; check 11 = value during parturition.

The number of patients with oedema remained constant (23) during the period of treatment, although its severity declined. Frusemide was given concomitantly to 17 patients. The laboratory values show a slight decrease in proteinuria.

The doses of guanfacine administered ranged from 1–4 mg daily, most patients being on 2 mg both initially (24 patients) and at parturition (17 patients).

Table 4 Mean ($\pm$ s.d.) maternal heart rate and supine blood pressure at the check before labour (check 10) and at the time of delivery (check 11)

	Check 10	Check 11
Supine blood pressure (mm Hg)		
Systolic	135.50	139.67
s.d.	± 5.92	± 5.71
Diastolic	88.00	91.33
s.d.	± 7.50	± 7.76
Supine heart rate (beats/min)	76.36	70.87
s.d.	± 5.47	± 5.03

Mean maternal heart rate and blood pressure (supine only) at the last check before labour and at the time of delivery are shown in Table 4. Comparing value no. 10 (last check before labour) with value no. 11 (value during delivery) using Wilcoxon's test for differences between pairs of observations, there was a slightly significant but clinically unimportant increase in mean systolic (4 mm Hg) and diastolic (3 mm Hg) blood pressures and a decrease of 6 beats/min in mean heart rate. At delivery (check no. 11) ten patients had a blood pressure exceeding 140/90 mm Hg as opposed to six at check no. 10 before labour.

The six cases of Caesarean section were all performed because of suspected placental insufficiency, later confirmed morphologically and histologically.

At blood pressure checks following delivery two women were found to have a persistently increased systolic blood pressure of up to 140 mm Hg. Early development of the infants was normal. Following delivery three patients were sent for further treatment to a specialist in internal medicine on the basis of earlier pathological laboratory findings. There were no withdrawals or drop-outs.

Discussion and Conclusions

Thirty pregnant women aged 22–34 yr presenting with pre-eclampsia were treated with guanfacine (mainly 2 mg daily) for 16–68 days. Seventeen of the patients were also given frusemide. From the first week of treatment there was a statistically significant and clinically relevant decrease in blood pressure. By the time labour started the blood pressure of 24 patients had returned to normal. During labour and the immediate postpartum period blood pressure increased again slightly in two cases.

Four days postpartum all the patients had normal blood pressures. There was no change in the number of patients with oedema, but the degree of oedema declined. Four days following parturition oedema was no longer present in any of the patients. Proteinuria similarly declined only slightly in the prepartum phase, but had disappeared in all but one case by 2 weeks after discharge.

Twenty-five of the patients reported a total of 46 side-effects (sedation in 25, dryness of the mouth in 15, and dizziness in 6 cases).

No significant changes were observed in foetal heart rate up to the time of labour. Thirty infants were born, 19 spontaneously, 5 by vacuum extraction and 6 by Caesarean section due to suspected placental insufficiency. Six were "small-for-date" babies, two having to be transferred to the children's unit. All developed normally later.

In the absence of a reference sample of patients it is not possible to assess whether guanfacine had any effect on the incidence of surgical delivery. It did, however, provide good control of pre-eclampsic hypertension in 23 cases, in the 'best responders' as little as 48 h after the first dose. Compared with other treatments traditionally used to control this condition (notably antihypertensive agents by intravenous administration), guanfacine has the advantage of being an easily manageable oral drug which, particularly during the ambulant prepartum phase, makes things considerably easier for both the patient and the doctor. The sedation to which guanfacine gave rise (in 25 cases) is not only desirable in the pre-eclampsic phase, but is in any case only disturbing

with doses higher than 2 mg daily. Where such doses are necessary, pre-eclampsia is probably serious enough to warrant admission, when sedation is not likely to cause treatment withdrawal.

These impressions of guanfacine are based on the open treatment of only 30 patients and could be made more objective by means of a controlled trial comparing guanfacine with an existing antihypertensive agent in common clinical use.

No signs of overdosage were observed and nothing was seen to suggest that contra-indications or special precautions might be necessary with guanfacine. There were no drop-outs and no cases of treatment withdrawal. Guanfacine was generally well tolerated.