Effectiveness of Atenolol in the Treatment of Hypertension During Pregnancy


This study assessed the effectiveness of atenolol in the treatment of moderate and severe hypertension during pregnancy. Seventy patients (mean age, 30.3±6.0 years), 35.7% primiparous, were included. Three groups were formed according to Davey and MacGillivray’s classification: 1) chronic hypertension without proteinuria (12 patients), 2) gestational hypertension without proteinuria (52 patients), and 3) preeclampsia (six patients). Treatment with atenolol was started when blood pressure was 150/100 mm Hg or higher after 48 hours’ rest. The treatment lasted at least 1 week; follow-up was every 2 weeks up to week 36, and from then on, weekly up to delivery. If blood pressure exceeded 160/110 mm Hg and the fetus was not yet mature, a second drug was added. A significant decrease in blood pressure was observed in the three groups (group 1: 155.8 ±15.0/100.8 ±7.6 versus 135.0 ±12.9/85.0 ±6.7 mm Hg; group 2: 154.2 ±13.6/104.9 ±9.3 versus 129.6 ±10.2/83.7 ±9.1 mm Hg; group 3: 158.3 ±27.1/104.1 ±8.0 versus 129.1 ±6.6/87.5 ±6.1 mm Hg). The doses of atenolol were 62.5±23.0 mg/day in group 1, 70.0±30.0 mg/day in group 2, and 100.0±41.0 mg/day in group 3. There was no fetal mortality. No significant difference occurred in newborn body weights. Four babies from group 2 mothers had an Apgar score of less than 7 at 1 minute, but only one remained abnormal after 5 minutes. In the same group, three cases of respiratory distress were observed. The rate of adverse effects was very low (one subject had orthostatic hypotension and another one bronchospasm), and they disappeared when the doses were reduced. Atenolol proved to be useful in the handling of hypertension during pregnancy. (Hypertension 1992; 19[suppl II]:H-129–H-131)

Hypertensive disease during pregnancy is one of the greatest challenges to the skills of obstetricians and internists. Preeclampsia occurs in 7-10% of all pregnancies, with a higher incidence in primiparas, twin pregnancies, or women over 35 years of age. The terminology used to describe it has been confusing and inconsistent, with more than 60 names in English and 40 in German. Blockers have been used in several trials during the past few years. Their use, however, has always been controversial. It is important to point out that there has been a lower incidence of the appearance of proteinuria whenever atenolol has been used. Blockers have been classified by their degree of cardioselectivity, intrinsic sympathomimetic activity, and lipophilicity/hydrophilicity. Atenolol is a cardioselective β-blocker that acts mainly on β1-receptors, most of which are in the myocardium. Most of the β1-receptors are in the uterus, bronchial tubes, and endocrine pancreas. Therefore, atenolol is less likely to act on uterine activity or produce bronchospasm.

The aim of this trial was to assess the efficacy and safety of atenolol in the treatment of moderate and severe arterial hypertension during pregnancy.

Methods

Seventy patients were recruited consecutively from March 1989. They were grouped according to the classification suggested by Davey and MacGillivray as follows: group 1: chronic arterial hypertension without proteinuria (12 patients); group 2: gestational hypertension without proteinuria (52 patients); and group 3: preeclampsia (six patients). None of the patients had developed superimposed preeclampsia. The criteria for entry were blood pressure between 140 and 170 mm Hg systolic or between 100 and 110 mm Hg diastolic after 48 hours’ rest on two occasions separated by 6 hours. Blood pressure was always measured on the same arm, with patients sitting. The fifth phase of Korotkoff was used to record diastolic pressure. All of these measurements were made with a mercury sphygmomanometer. Proteinuria was considered positive when it was greater than or equal to 0.5 g/24 hr (Exton Rase method).
TABLE 1. Maternal Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>34.6±6.7</td>
<td>31.3±5.3</td>
<td>26.9±7.1</td>
</tr>
<tr>
<td>Primiparas</td>
<td>2 (16.7%)</td>
<td>19 (36.5%)</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td>Drug started (wk)</td>
<td>24.5±10.0</td>
<td>29.8±9.4</td>
<td>31.0±8.2</td>
</tr>
<tr>
<td>SBP, predrug (mm Hg)</td>
<td>155.8±15.0</td>
<td>154.2±13.6</td>
<td>158.3±27.1</td>
</tr>
<tr>
<td>Postdrug (mm Hg)</td>
<td>135.0±12.9*</td>
<td>129.6±10.2†</td>
<td>129.1±6.6‡</td>
</tr>
<tr>
<td>DBP, predrug (mm Hg)</td>
<td>100.8±7.6</td>
<td>104.9±9.3</td>
<td>104.1±8.0</td>
</tr>
<tr>
<td>Postdrug (mm Hg)</td>
<td>85.0±6.7†</td>
<td>83.7±9.1†</td>
<td>87.5±6.1§</td>
</tr>
<tr>
<td>Dose of atenolol (mg/day)</td>
<td>62.5±23.0</td>
<td>70.0±30.0</td>
<td>100.0±41.0</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cesarean</td>
<td>9 (75%)</td>
<td>31 (60%)</td>
<td>6 (100%)</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure.

*p<0.005, †p<0.001, ‡p<0.05, §p<0.01.

The starting 50-mg daily dose of atenolol was progressively increased until diastolic blood pressure reached a range between 90 and 95 mm Hg to avoid a significant decreased uteroplacental blood flow or when a dose of 150 mg daily was reached. All patients received atenolol for at least 1 week and were seen every 15 days up to week 36 and then weekly until the end of pregnancy. When ever possible, treatment was stopped 2–4 days after delivery. Laboratory tests (red and white cell counts, blood glucose, serum urea, creatinine, liver enzymes, 24-hour proteinuria) were done monthly until week 36 and every 2 weeks from then onward. If any anomaly was observed, these tests were performed again. Those patients who had any contraindication to the use of β-blockers (heart failure, bronchial asthma, atrioventricular block) were excluded. A second drug, nifedipine, was added in seven patients during follow-up when blood pressure was greater than or equal to 160/110 mm Hg and the fetus was still immature.

Neonates were seen by the neonatologist (C.M.). The following parameters were recorded: newborn weight, Apgar score at 1 and 5 minutes, respiratory distress syndrome, Capurro index, 5 blood glucose during the first 24 hours, and fetal mortality. Blood glucose was determined by Destrotix at 1, 4, 6, 12, and 24 hours and was confirmed by formal analysis if it was less than 1.4 mmol/l. The neonatologist decided when the newborns could be discharged. At present, the newborns are still being followed up.

After the patients had been informed about the risks and benefits of the use of atenolol, they gave their consent to take part in this study. The t test for paired samples was used for statistical evaluation.

Results

Results are presented in Tables 1 and 2. Patients showed good tolerance to atenolol. Only two of them had side effects (bronchospasm and orthostatic hypotension), which disappeared when the dose was decreased. Group 3 had the largest number of youngest women and primiparas (67%). Blood pressure decreased significantly in the three groups (group 1: 155.8±15.0/100.8±7.6 versus 135.0±12.9 [p<0.005]/85.0±6.7 [p<0.001] mm Hg; group 2: 154.2±13.6/104.9±9.3 versus 129.6±10.2/83.7±9.1 [p<0.001] mm Hg; group 3: 158.3±27.1/104.1±8.0 versus 129.1±6.6 [p<0.05]/87.5±6.1 [p<0.01] mm Hg). The atenolol dosages administered to each group were 62.5±23.0 mg/day, 70.0±30.0 mg/day, and 100.0±41.0 mg/day, respectively. They were started at week 24.5±10.0 in group 1, 29.8±9.4 in group 2, and 31.0±8.2 in group 3.

Newborn weights were 2,901.8±1,018 g in group 1, 3,059.4±665.2 g in group 2, and 2,431.0±648.5 g in group 3, which had no significant statistical relevance. Four babies of group 2 mothers had an Apgar score less than 7 at 1 minute, but they were normalized at 5 minutes in all except one. Another three babies of the
same group developed transient respiratory distress syndrome, but they did not require ventilation. The Capurro index was 38.8±9.0, 38.7±1.4, and 35.2±3.4 in groups 1–3, respectively. There was no fetal mortality. The rate of cesareans was nine (75%) in group 1, 31 (60%) in group 2, and six (100%) in group 3.

Discussion

Hypertension during pregnancy is a serious disease, continuing to be the major cause of fetal and maternal morbidity and mortality. In a medical report published in London in 1986, hypertension was reported to account for 20% of maternal mortality. What is even more surprising, as Rubin points out, is that most of these deaths could have been avoided. Two types of hypertension complicate pregnancy, the more common being that induced by pregnancy. It develops during the last trimester and carries a substantial risk to the fetus if accompanied by proteinuria (preeclampsia). The other type is hypertension that is present at the beginning of pregnancy. Most of the time, this type of hypertension does not cause serious complications if it is mild or moderate, but it can involve risks with the appearance of proteinuria and evolve into superimposed preeclampsia, which is the clinical manifestation with the worst fetal prognosis. The correct classification of patients is essential for adequate handling and interpretation of results. The classification proposed by Davey and MacGillivray has been adopted for this study and is based on signs of hypertension and proteinuria that are easily quantifiable and unequivocal.

The use of β-blockers during pregnancy has always been, and still is, a controversial issue. The first trials in which β-blockers were given were rather discouraging, because there was a high incidence of intrauterine growth retardation and fetal mortality; however, these trials were based on case reports and were retrospective. Furthermore, prospective and randomized reports were published showing the efficacy of atenolol in lowering blood pressure and reducing the development of proteinuria. It is also important to stress that the newborns that were followed in the first year of life developed completely normally.

In a recent trial, 33 essential hypertensive women were studied during pregnancy. Atenolol was given from the end of the first trimester to patients with mild hypertension. The newborns presented intrauterine growth retardation. Our results do not agree with those of Rubin, which could be because of the smaller doses of atenolol we gave to maintain diastolic blood pressure between 90 and 95 mm Hg to avoid a significant decrease in utero-placental blood flow.

Proteinuria is a very important parameter. Its presence indicates renal damage, and its appearance worsens the prognosis. Atenolol proved to lower its incidence. In an earlier trial carried out with metyl-dopa, the incidence of preeclampsia was 27% and of superimposed preeclampsia was 5%, as opposed to a preeclampsia rate of 8.5% with atenolol. Cardiac output in normal pregnancy is increased by approximately 40% above normal values. Glomerular filtration rate expands by 50%. This is largely accomplished by an increase in renal plasma flow. These hemodynamic conditions are associated with a threefold increase in albumin excretion. Easterling and Benedetti suggest that preeclampsia is the result of an exaggeration of these physiological stresses during pregnancy leading to a hyperdynamic condition. Atenolol acts as an antihypertensive agent by reducing cardiac output. Associated with the decline in cardiac output is a parallel reduction in renal plasma flow. It is important to point out that once renal damage has been produced, it does not disappear with the use of atenolol.

In conclusion, atenolol proved to be an effective drug in the treatment of moderate and severe hypertension during pregnancy and in the reduction of the appearance of proteinuria, having mild adverse effects on the mothers and newborns.

References


KEY WORDS: pregnancy-induced hypertension • proteinuria • atenolol
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G Fabregues, L Alvarez, P Varas Juri, S Drisaldi, C Cerrato, C Moschettoni, D Pituelo, H P Baglivo and R J Esper

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