Cardiovascular Response to Adrenergic Stimulation during Treatment with Tertatolol

A New Non-Cardioselective Beta-Blocking Agent in Primary Hypertensive Patients

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SUMMARY

The antihypertensive effects of tertatolol, a new non-cardioselective beta-blocking drug, were investigated in 20 patients with mild to moderate primary arterial hypertension, in a placebo controlled double blind randomized study. After tertatolol 5 mg o.d. significant decreases in both systolic and diastolic blood pressure and in heart rate were observed at rest (BP from 155/103±3/1 to 139/91±4/3 mmHg p<0.01; HR from 79±2 to 60±2 bpm p<0.01). Peak blood pressure, heart rate and myocardial O2 consumption, indirectly measured as cardiac workload, determined during adrenergic stimulation by 70° head-up tilt, cold pressor test, mental arithmetic stress, isometric exercise and bicycle exercise were also reduced by 4 weeks of tertatolol treatment in comparison to pre-treatment levels. No significant changes in the same parameters were induced by placebo. No side effects were observed during treatment.

Additional Indexing Words:
Tertatolol Beta blockers Primary hypertension Cardiovascular system Adrenergic stimulation

ETA blockers are useful as first line agents in the treatment of arterial hypertension, as shown by several studies published in the last 10 years.1),2)

Compounds with different characteristics with respect to selective B1 antagonism, intrinsic sympathetic activity (ISA) and hydro or liposolubility are available. Tertatolol is a new, long acting non-cardioselective beta-blocking agent devoid of ISA3)-5) with beneficial, or at least no detrimental, effects on renal perfusion,6)-9) which has been shown to reduce significantly

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resting blood pressure in animal\textsuperscript{10} and human studies.\textsuperscript{11}

However, the variability of blood pressure (BP) over 24 hrs, largely dependent on the activity of the subjects, is well known. Blood pressure in fact has been found to be lower during sleep and higher during stressful situations such as work or a visit to the outpatient clinic.\textsuperscript{12} In order to evaluate whether tertatolol is also able to lower BP during stress, we have investigated in essential hypertensive patients cardiovascular responses to more than one laboratory test stimulating the adrenergic nervous system. Therefore in a randomized, double blind, placebo-controlled clinical trial, blood pressure, heart rate and cardiac workload, an indirect measure of myocardial O\textsubscript{2} consumption, were investigated at rest and during 70° head-up tilt, cold pressor test, mental arithmetic stress, and isometric and bicycle exercise, all of which are highly reproducible laboratory tests that enhance sympathetic stimulation of the cardiovascular system.

**Patients and Methods**

Twenty patients (12 males, 8 females), age range 18–57 yrs (mean 39±10) with essential hypertension of mild to moderate degree entered the study.

Criteria for exclusion were:

a) secondary hypertension assessed by i.v. pyelography, serum electrolytes, plasma renin activity, serum aldosterone, urinary catecholamines;

b) cardiovascular diseases (heart failure, left ventricular dilatation, A-V block, myocardial infarction or stroke in the last 6 months, bradycardia);

c) chronic diseases such as liver cirrhosis, renal failure, asthma, peptic ulcer;

d) metabolic diseases such as obesity, gout, diabetes mellitus;

e) history of severe side effects with other beta blockers;

f) pregnancy, lactation or use of oral contraceptives.

Patients selected for the trial were informed of the aim of the study and their consent was requested and obtained. At this stage any antihypertensive treatment was withdrawn, and a well balanced isocaloric diet without salt intake restriction was prescribed for a 4 week wash-out period during which a single daily oral dose of placebo was given. At the end of the wash-out period, patients still fulfilling the study criteria were randomly prescribed either tertatolol 5 mg o.d. or placebo 1 tablet o.d. for a 4-week period, according to a double blind model.

At the end of the wash-out and treatment periods systolic (SBP) and diastolic (DBP) blood pressure, heart rate and cardiac workload ($CW=SBP\times HR$) were measured:
1) at rest in the supine position and after 2 and 5 min standing, by an automatic device (Sentron, Bard Biomedical);

2) during a 5-min 70° head-up tilt and in the following recovery phase;

3) during a 2-min cold pressor test, performed by immersing one hand to just above the wrist in iced water at 4 to 5°C, and in the following recovery phase;

4) during 3 min of isometric exercise and in the following 5-min recovery phase. The test was performed by squeezing the handgrip at 30% of the maximal stress;

5) during a 4-min mental stress test, performing simple oral calculations at 5-sec intervals while a standardized noise was produced by a metronome;

6) during 10 min of submaximal exercise on a bicycle and in the following 5-min recovery phase. After a 2-min warm-up at 40 watts, the load was progressively increased by 30-watt increments until a load of 100 watts was reached. At this stage the exercise was sustained for 5 min.

During each test BP was measured 3 times at rest, at each minute of the stress test, and after 2 and 5 min in the recovery phase. Resting BP and HR (mean of 3 measurements), steady-state BP and HR during stress (average of all measurements performed during the test), BP and HR in the recovery phase (mean of 2 measurements) were included in the analysis of the cardiovascular response to the tests.

Statistical analysis: Results are expressed as mean ± standard deviation. The statistical analysis was performed by two-way analysis of variance with Tukey's multiple comparisons.

RESULTS

Body weight of the tertatolol group was 73±15 kg at baseline and 73.8±14 kg at the end of the double blind study. In the placebo group body weight was 72±13 kg at baseline and did not change after treatment. A significant decrease was observed in supine and standing blood pressure and in heart rate at rest, 24 hrs after the last dose of tertatolol, while placebo did not induce any change on the same parameters (Table I).

During 70° head-up tilt SBP, DBP, HR and CW were reduced by tertatolol in comparison to pretreatment values, the decrease being of the same magnitude as that observed at rest (153/96±14/8 and 148/93±9/7 mmHg at 1 and 5 min after tilting before tertatolol, 139/87±13/9 and 129/80±12/14 mmHg at the same times after tertatolol) (Fig. 1). In the placebo group BP was 152/105±13/19 and 153/97±18/14 mmHg at 1 and 5 min after tilting.
Table I. Blood Pressure and Heart Rate at Rest at Baseline (T0) and after 15 (T15) and 30 (T30) Days on Tertatolol or Placebo in 2 Groups of Hypertensive Patients

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T15</th>
<th>T30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td><strong>155±3</strong></td>
<td><strong>140±5</strong></td>
<td><strong>139±4</strong></td>
</tr>
<tr>
<td>tertatolol</td>
<td>154±4</td>
<td>158±8</td>
<td>153±5</td>
</tr>
<tr>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td><strong>103±1</strong></td>
<td><strong>91±4</strong></td>
<td><strong>91±3</strong></td>
</tr>
<tr>
<td>tertatolol</td>
<td>105±2</td>
<td>108±3</td>
<td>106±3</td>
</tr>
<tr>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td><strong>79±2</strong></td>
<td><strong>65±5</strong></td>
<td><strong>60±2</strong></td>
</tr>
<tr>
<td>tertatolol</td>
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<td>77±3</td>
</tr>
<tr>
<td>placebo</td>
<td></td>
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</table>

Significance vs placebo. ** p<0.01.

Before treatment; after treatment at the same times BP was 159/108±19/13 and 158/103±27/11 mmHg.

During the cold pressor test BP in the tertatolol group increased from 160/93±9/9 to 168/103±11/11 mmHg before and from 146/87±16/8 to 163/92±24/13 mmHg on treatment. Heart rate and cardiac workload during
Fig. 2. Systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and cardiac workload (CW) during cold pressor test before (open circles) and after (closed circles) 5 mg o.d. tertatolol in 10 hypertensive patients.

Fig. 3. Systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and cardiac workload (CW) during mental arithmetic stress before (open circles) and after (closed circles) 5 mg o.d. tertatolol in 10 hypertensive patients.

this test were significantly reduced by tertatolol (Fig. 2). Placebo did not induce any change in these parameters. In the tertatolol group the percent peak increase from resting BP was 5/11% at baseline and 12/7% on treatment; in the other group it was 7/10% and 6/3%, respectively before and after placebo administration. Reduction in heart rate at each time of testing during tertatolol was significantly different from that on placebo, while BP changes reached statistical significance only in the recovery phase, despite a marked fall also at baseline and during the test.

During mental arithmetic stress, peak blood pressure, heart rate and cardiac workload were significantly reduced by tertatolol. In particular, SBP increased from 150/92±10/10 to 171/108±17/13 mmHg before treatment and from 137/81±10/12 to 156/90±20/11 mmHg on the active drug
Fig. 4. Systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and cardiac workload (CW) during handgrip before (open circles) and after (closed circles) 5 mg o.d. tertatolol in 10 hypertensive patients.

Fig. 5. Systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and cardiac workload (CW) during bicycle exercise before (open circles) and after (closed circles) 5 mg o.d. tertatolol in 10 hypertensive patients.

(Fig. 3). In the control group the increase was from 152/96±20/10 to 163/103±24/17 mmHg before and from 143/96±26/15 to 154/100±20/14 mmHg on placebo. Systolic and diastolic blood pressure at the peak of the test changed from resting values by 10/16% before tertatolol and by 9/10% after drug; in the placebo group the same parameters increased by 7/7% and 12/4% before and after treatment, respectively.

During 30% maximal handgrip DBP, HR and CW were at lower levels when patients received tertatolol than at pretreatment. SBP during the test on the other hand, was only slightly modified by the therapy (Fig. 4). No change was observed in the same parameters in the placebo group in comparison to pretreatment values. Percent peak changes from resting SBP and DBP in the tertatolol group were of the same magnitude before and after treatment (17/23% vs 21/26%); similar increases were observed in the placebo group (18/25% vs 12/10% before and after treatment, respectively).
During bicycle exercise, diastolic blood pressure was not reduced by tertatolol; a more marked effect was, on the other hand, observed on systolic blood pressure, heart rate and cardiac workload (Fig. 5). Placebo did not influence blood pressure (at the beginning of exercise 161/103±17/12 mmHg before and 157/112±18/17 after placebo; at the end of exercise 200/110±14/10 mmHg and 197/115±16/16 before and after placebo, respectively) and cardiac workload (at the beginning of exercise 12,871 vs 12,428 before and after treatment, respectively; at the end of exercise 26,071 vs 24,257 before and after treatment, respectively). During this test the percent peak change for SBP and DBP was 26/6% before and 23/10% after tertatolol; the same parameters changed by 24/7% and 25/3% before and after placebo, respectively.

**Discussion**

It is generally agreed that beta blockers are more active in hypertensive patients with hyperactivity of the adrenergic nervous system, while vasodilators seem to decrease BP particularly in patients with low sympathetic activity. This study was designed to evaluate whether the new beta-blocker tertatolol, non-cardioselective and devoid of ISA, was able to affect cardiovascular responses to well known and validated adrenergic stimuli, highly reproducible in a clinical laboratory.

It is known that there are sex-related differences in the geometry of large arteries, including the brachial artery, which may account for a different hemodynamic response to cardiovascular stimulation in men and women. However, in our group the response pattern was similar in both sexes as shown by a separate analysis of data; we have therefore decided to pool data from male and female patients. The design of the study allowed that each patient represented his own control and both the tertatolol and placebo groups had the same number of men (6 for each group) and women (4 for each group). In order to explain the lack of sex-related differences in BP response, it is noteworthy to remark that the female patients were older than the males in both groups (45 vs 38 yrs in the tertatolol; 42 vs 39 yrs in the placebo group). Finally, when divided by sex, the sample size in each subgroup was too small for any statistical analysis.

Tertatolol was shown to induce at rest a significant decrease in systolic and diastolic blood pressure without any excessive reduction in heart rate, which was never depressed below 50 beats/minute.

Seventy degree head-up tilt is one of the tests exploring possible impairment of the baroreceptor response to changes in body position. It has
been found that some drugs such as prazosin, methyldopa and high-dose ketanserin may affect the pressure response to tilting with a marked BP fall compared to supine measurements. Middle-term tertatolol treatment, like placebo, did not impair the baroreceptor control of cardiovascular hemodynamics since BP and HR did not significantly change from the corresponding resting values. The differences at each time versus pretreatment only reflected the lower BP values observed in the supine position without further fall during the test. The mental arithmetic test is a submaximal mental stress test investigating the central adrenergic control of the cardiovascular system.\textsuperscript{18\textendash}20\textsuperscript{) }

Among the different laboratory tests stimulating the sympathetic nervous system, it is one of the most powerful predictors of absolute BP levels measured during a 24-hr period.\textsuperscript{12\textsuperscript{) }} The percent increase from preexercise values in systolic and diastolic BP on tertatolol was of a magnitude similar to that observed before treatment; peak levels however were largely affected by preexercise BP and therefore a marked reduction in BP, HR and CW resulted from treatment.

Handgrip isometric exercise requires a submaximal voluntary contraction, but its maintenance becomes increasingly difficult with time and leads to a real maximal contraction, producing an ever increasing vasomotor response.\textsuperscript{21\textendash}22\textsuperscript{) } The cardiovascular response during the test was similar before and after tertatolol. Again preexercise values markedly influenced the outcome of the test and therefore during tertatolol the peak BP, HR and CW levels were significantly reduced in comparison to pretreatment. Other beta blockers, such as propranolol have failed, up to now, to affect peak BP during this test, while the alpha-blocking agent prazosin was able to reduce the magnitude of the increase,\textsuperscript{23\textsuperscript{) }} supporting the hypothesis that only post-junctional alpha-receptors have an important relationship to pressure response to isometric handgrip.

Percent pressure increase during the cold pressor test on tertatolol was of the same magnitude of that observed before treatment; however resting BP was on the two occasions significantly different and therefore both BP and myocardial oxygen demand during this test were significantly reduced by beta blockade.

A similar trend was observed during bicycle exercise where, in particular, \( \text{O}_2 \) consumption in the myocardium was reduced by the active treatment. These results confirm previous observations with other beta-blocking agents of both cardio and non-cardioselective types.\textsuperscript{24\textendash}25\textsuperscript{) }

In conclusion, the results of this study indicate that this new beta blocker, like other older compounds of the same class, is able to reduce BP at rest.
and in response to different types of adrenergic stimulation and does not impair the baroreflex BP control during changes in body position.

The lack of untoward side effects, as already shown on renal hemodynamics unlike other beta blockers, and the long-lasting antihypertensive activity support the use of once daily tertatolol in the treatment of mild to moderate hypertension.

**References**

18. Harronymus HV, Boomma F, Veld AJ, Schalekamp M: Stress levels of adrenaline amplify
the blood pressure response to sympathetic stimulation. J Hypert 4: 255, 1986


