Effects of alpha-1 adrenergic receptor antagonist, terazosin, on cardiovascular functions in anaesthetised dogs

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Received 31 October 2003; revised 24 August 2004

Initially a dose-response curve of phenylephrine was constructed at dose strengths of 1-16 μg/kg in a cumulative manner. Phenylephrine caused a significant rise in the mean arterial pressure, left ventricular systolic pressure, left ventricular contractility, stroke volume and a significant decline in the heart rate. Terazosin was administered in three selected doses of 10, 100 and 300 μg/kg. Following each dose of terazosin, dose-response curve of phenylephrine was constructed. Terazosin, per se, decreased the basal mean arterial pressure, left ventricular systolic pressure, left ventricular contractility and stroke volume significantly in a dose dependent manner with an increase in the heart rate with no significant change in the cardiac output. The baroreflex sensitivity at all the three doses remained unchanged. In conclusion, the present findings support the view that terazosin reduces the blood pressure in a physiologically more favorable manner by maintaining the neural integrity of the cardiovascular system.

Keywords: Alpha-1 adrenergic receptor, Baroreflex, Left ventricular performance, Terazosin.

Hypertension is one of the commonest prevalent disorders in current times. It has been suggested that, even in hypertensives, the blood pressure regulatory mechanisms continue to operate although at a higher set point. Alpha-1 adrenergic antagonists, eg. terazosin, have been used as the mainstay of antihypertensive therapy. Stimulation of alpha-1 adrenergic receptors modulates various steps of the cardiac excitation-contraction coupling cascade including ionic conductances, cytosolic ionic activities and calcium sensitivity of contractile proteins. They also regulate the cardiac rhythm, conduction and force of contraction. However, no evidence is available regarding the effect of long term use of alpha-1 adrenergic blockers on the left ventricular performance and the neural regulation of blood pressure.

The function of myocardial alpha-1 adrenoceptors can be studied using selective alpha-1 adrenergic agonist (phenylephrine) and antagonist (terazosin). Phenylephrine by selectively stimulating alpha-1 adrenergic receptors, has been shown to produce a positive inotropic effect and an increase in the arterial blood pressure by causing peripheral vasoconstriction. Terazosin acts on the same peripheral receptors causing peripheral vasodilation and a fall in the arterial blood pressure. It also acts on the myocardial adrenoceptors leading to a decline in the left ventricular systolic pressure and contractility. Although effect of different doses of terazosin has been studied on blood pressure, left ventricular performance has not been assessed. In addition, its effect on the heart rate with the fall in the blood pressure needs to be examined as there are some reports of alpha-1 adrenergic antagonists (prazosin) interfering with the sensitivity of the baroreflex.

Therefore, in the present study, the effect of three different doses of terazosin, on the phenylephrine induced hemodynamic changes and the sensitivity of the baroreceptor mediated regulation of the arterial blood pressure have been studied.

Materials and Methods
All experiments were approved by the V P Chest Institute Ethical Committee and were performed...
under the guidelines of Care and Use of Experimental Animals. Healthy, male, mongrel dogs (10) weighing between 12-14 kg were anaesthetized with sodium pentobarbitone (35 mg/kg, iv). Trachea was cannulated, polyethylene catheters were placed in the femoral artery to record blood pressure using (Statham P32 Db) pressure transducer and in the femoral vein for injecting drugs. Another catheter was placed in the left ventricle through the left common carotid artery for recording left ventricular pressure with a pressure transducer (Statham P32 Db). The pressure recording system was calibrated with a mercury manometer before each experiment. The left ventricular pulse was electronically differentiated (Differentiator Contractility-Lectromed model-5270) to record left ventricular dP/dt and also to drive a cardiographometer (Lectromed-model-5260) to record the heart rate. All these variables were recorded on a polygraph (Lectromed-UK). Room temperature was maintained at 25°±2°C. The body temperature of the animal was recorded with a rectal thermometer and was maintained between 37°-38°C. Arterial blood samples were withdrawn from the femoral artery for measurement of gases (Eischweiler BGA plus E-Model Type 331). The blood gases were kept in the normal range throughout the experiment. After surgical procedures, the animal was allowed to stabilize for 30 min before taking observations.

Measurement of cardiac output and stroke volume—Cardiac output was measured by the thermodilution technique using a cardiac output computer (COM-1 Edward Company USA). Cardiac output was measured before terazosin treatment (control) and subsequently after each dose of terazosin (10, 100 and 300 µg/kg). Stroke volume was calculated as cardiac output/heart rate.

Calculation of baroreflex sensitivity—Arterial baroreceptor mediated regulation of arterial pressure (Baroreflex) was calculated from the mean arterial pressure—Cardiac output/heart rate which was significant (P<0.05) only at higher concentrations (100 and 300 µg/kg) (Fig. 3). Terazosin attenuated the phenylephrine induced rise in the arterial pressure (Figs 1 and 2) and the fall in the heart rate which was significant (P<0.05) at the dose strengths of 100 and 300 µg/kg (Fig. 3).

Terazosin caused a fall in the LVSP which was significant (P<0.05) at the dose strengths of 100 and 300 µg/kg (Fig. 4). Control value of LVSP was

and terazosin (Sigma Chemicals) were freshly prepared by dissolving in distilled water. Following control recording of all the haemodynamic parameters, a cumulative dose response curve of phenylephrine (1-16 µg/kg) was determined for all the parameters. After 20 min, terazosin (10 µg/kg) was injected and the effects were recorded. The phenylephrine dose response observations were repeated with a maximum strength of 32 µg/kg. After recovery from the phenylephrine effect, a higher dose of terazosin (100 µg/kg) was administered and dose response curve of phenylephrine at a maximum dose of 64 µg/kg was obtained. After a recovery period of 30 min, the highest dose of terazosin (300 µg/kg) was administered and dose response curve of phenylephrine at a maximum dose of 128 µg/kg was constructed. The highest dose of phenylephrine after each dose of terazosin was selected to produce a 50–70% rise in the arterial pressure.

Statistical analysis—The data are expressed as mean±SE. One-way ANOVA followed by Newman-Keuls test was used for statistical analysis. P<0.05 was considered significant.

Results

Effect of terazosin on blood pressure and heart rate—Intravenous administration of phenylephrine produced a dose-dependent rise in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and mean arterial pressure (MAP) (Figs 1 and 2) and a corresponding fall in the heart rate (HR) (Fig. 3).

Terazosin at all the three doses (10, 100 and 300 µg/kg) produced a significant (P<0.05) dose-dependent fall in the basal values of all the parameters of arterial blood pressure (Figs 1 and 2) and a rise in the heart rate which was significant (P<0.05) only at higher concentrations (100 and 300 µg/kg) (Fig. 3).

Terazosin attenuated the phenylephrine induced rise in the arterial pressure (Figs 1 and 2) and the fall in the heart rate (Fig. 3) at all the three doses. This effect of terazosin was found to be dose-dependent.

Effect of terazosin on left ventricular pressure and left ventricular dP/dt max—On injection of phenylephrine in progressively increasing doses (1-16 µg/kg), there was a corresponding rise in both left ventricular systolic pressure (LVSP) and left ventricular dP/dt max (Fig. 4).

Terazosin caused a fall in the LVSP which was significant (P<0.05) at the dose strengths of 100 and 300 µg/kg (Fig. 4). Control value of LVSP was
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Fig. 1—Effect of progressively increasing doses of phenylephrine (1-16 μg/kg) on Systolic blood pressure (A) and diastolic blood pressure (B) before (○) and after pretreatment with three different doses [10(●), 100(▲) and 300(●)] μg/kg of terazosin. *P<0.05 denotes significantly different from respective control value. All values are mean±SE from 10 dogs.

Fig. 2—Effect of progressively increasing doses of phenylephrine (1-16 μg/kg) on Pulse pressure (A) and mean arterial pressure (B) before and after pretreatment with three different doses [10(●), 100(▲) and 300(●)] μg/kg of terazosin. *P<0.05 denotes significantly different from respective control (○) values. All values are mean±SE from 10 dogs.

201±4 mmHg. Terazosin produced a fall of LVSP to 185±5, 180±7, and 178±5 mmHg at 10, 100 and 300 μg/kg respectively (Fig. 4). Phenylephrine induced rise in LVSP was significantly (P<0.05) attenuated after terazosin (100 and 300 μg/kg).

LV dP/dt max also showed a significant (P<0.05) fall at the dose strengths of 100 and 300 μg/kg of

Fig. 3—Inhibition of phenylephrine induced dose-dependent response in Left ventricular systolic pressure (LVSP, A) and left ventricular contractility (LV d P/dt max, B) by terazosin in three different doses [10(●), 100(▲) and 300(●)] μg/kg. Post-terazosin values for LVSP and LV d P/dt max were compared with the respective control value (○). *P<0.05 denotes significantly different from respective control value. All values are mean±SE from 10 dogs.

Fig. 4—Effects of terazosin in three different doses [10(●), 100(▲) and 300(●)] μg/kg on fall in heart rate produced by phenylephrine (PE). Post-terazosin values of HR after individual dose of PE were compared with the respective control value (○). *P<0.05 denotes significantly different from respective control value. All values are mean±SE from 10 dogs.
terazosin (Fig. 4). From a control value of LV $dP/dt_{\text{max}}$ of $4034\pm115$ mmHg, terazosin produced a fall in LV $dP/dt_{\text{max}}$ to $4030\pm116$, $4027\pm115$, and $4024\pm117$ mmHg at 10, 100 and 300 $\mu$g/kg respectively (Fig. 4).

Terazosin significantly ($P<0.05$) attenuated the phenylephrine induced rise in LV $dP/dt_{\text{max}}$ at the dose strengths of 100 and 300 $\mu$g/kg.

**Effect of terazosin on stroke volume**—Stroke volume was calculated as the cardiac output divided by the heart rate (CO/HR) after each dose of terazosin. The control value of stroke volume was $10.45\pm0.5$ ml. Following the first dose of terazosin (10 $\mu$g/kg), there was a small fall in the value to $10.18\pm0.4$ ml (Fig. 4A). After the second (100 $\mu$g/kg) and third (300 $\mu$g/kg) doses the fall in the stroke volume was significant ($P<0.05$) the values being $9.04\pm0.3$ and $8.87\pm0.2$ ml respectively (Fig. 4A).

**Effect of terazosin on cardiac output**—The basal value of the cardiac output (CO) was $1.53\pm0.2$ L/min. After the first dose of terazosin (10 $\mu$g/kg), there was no change in the CO (Fig. 5B). With the second (100 $\mu$g/kg) and the third (300 $\mu$g/kg) dose, the cardiac output was $1.53\pm0.4$ and $1.54\pm0.3$ L/min respectively (Fig. 5B).

**Effect of terazosin on baroreflex sensitivity**—Baroreflex sensitivity calculated from MAP-HR curves for control was $2.78\pm0.2$ beats/min/mmHg (Fig. 6). Baroreflex sensitivity for 10 $\mu$g/kg of terazosin was $2.82\pm0.3$ and for 100 $\mu$g/kg and 300 $\mu$g/kg of terazosin, it was $2.76\pm0.2$ and $2.81\pm0.3$ (Fig. 6) respectively. There was no significant difference between control and post-terazosin baroreflex sensitivity values.

**Discussion**

Phenylephrine, as expected, induced a significant pressor response in a dose-dependent manner and a corresponding decline in the heart rate via the arterial baroreceptor pathway. These effects were significantly attenuated by terazosin administration which was related to the dose strength. Terazosin is known to block the post-synaptic vascular alpha-1 receptors leading to a decreased vascular resistance and the subsequent vasodilatation produces a fall in the blood pressure. A corresponding rise in the heart rate with the fall in the blood pressure was observed demonstrating an active baroreflex mechanism compensating for the decline in blood pressure as well as to restore the normal pressure. The baroreflex sensitivity calculated at all the three doses of terazosin did not show any significant change as compared to the control value. This suggests that terazosin lowers blood pressure in a physiologically favorable manner maintaining the normal baroreceptor regulatory response.

Left ventricular performance was similarly enhanced by phenylephrine as evidenced by a rise in
left ventricular systolic pressure and left ventricular dP/dt (max). A significant fall in both left ventricular systolic pressure and dP/dt (max) by terazosin, suggests an important role of myocardial alpha-1 adrenoceptors in the genesis of the positive inotropic effect. Terazosin did not produce any significant change in the cardiac output which could be partly due to an increase in the heart rate inspite of the fall in the stroke volume produced by terazosin.

Terazosin was administered in three different doses of 10, 100 and 300 µg/kg. Though the drug demonstrated its alpha-1 blocking properties at all the three doses, the optimal response was produced at the strength of 100 µg/kg. Hence, the dose strength of 100 µg/kg can be considered as the optimal dose.

In conclusion, terazosin acts as a potent antihypertensive by inhibiting peripheral alpha-1 adrenoceptors thereby producing a fall in peripheral resistance and subsequently blood pressure. Inspite of a significant negative inotropic effect along with its antihypertensive action, terazosin did not produce any fall in the cardiac output and the baroreflex regulatory mechanism remained unaffected which can be considered as an additional advantage of the drug.

References
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