Alfuzosin and the venous reflex response: studies in normal subjects

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- 1 Alfuzosin is a post-synaptic α -adrenoceptor antagonist with antihypertensive and peripheral vasodilator properties.
- 2 We measured the effect of alfuzosin, 5 mg, on sympathetically-mediated venoconstriction by changes in the venous reflex response (VRR) in a randomised, double-blind, placebo-controlled, crossover study in a group of 10 healthy volunteers.
- 3 There was a significant inhibition of the VRR after alfuzosin compared with placebo ($P < 0.001$) which was present 1 h after the dose and still evident at 6 h.
- 4 Supine blood pressure was significantly lower ($P < 0.01$) and supine heart rate was significantly higher ($P < 0.001$) after alfuzosin compared with placebo.
- 5 Inhibition of the VRR by alfuzosin was observed to precede the development of reflex tachycardia.

Keywords venous reflex response alfuzosin placebo

Introduction

Peripheral venous tone is considered to be maintained by the activity of the noradrenergic sympathetic nervous system (Shepherd & Vanhoutte, 1978), and a reduction in venous tone can sometimes be sufficient to cause major and symptomatic falls in arterial blood pressure (Muller-Rucholtz *et al.*, 1979). The venous reflex response (VRR) is considered to be an effective method for assessing noradrenergic systemic venoconstrictor tone (Samueloff *et al.*, 1966; Epstein *et al.*, 1968). Attenuation of the VRR has been shown to parallel the reduction in blood pressure during guanethidine therapy (Walter *et al.*, 1975) and has been associated with postural hypotension and syncope ('first dose' phenomenon) following prazosin (Schapel & Betts, 1981). Alfuzosin, a 1,3 diaminopropane derivative, is a selective post-synaptic α_1 -adrenoceptor antagonist with both antihypertensive and peripheral vasodilator properties.

We decided to study the effect of alfuzosin on

sympathetically-mediated venoconstriction by measurement of the VRR in a group of healthy volunteers.

Methods

Ten healthy volunteers (4M, 6F, aged 21–39 years, all within 10% of ideal body weight) took part in this randomised, double-blind crossover study in which they received single oral doses of alfuzosin, 5 mg, or placebo on separate occasions 1 week apart. The study protocol was approved by the Ethics Committee of St Bartholomew's Hospital, London.

Measurements

Supine systolic and diastolic blood pressure using standard mercury-in-glass sphygmomanometry taking phase V of the Korotkov

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Figure 1 Mean supine blood pressure before (time 0) and after treatment with alfuzosin (●) and placebo (■).

sounds as the diastolic pressure, heart rate by palpation of the radial artery over 30 s, and VRR were measured before treatment and at 20 min intervals for 6 h after each dose. All procedures were carried out in a quiet, draught-free room with the ambient temperature maintained at 20°C. The subjects remained supine from at least 20 min before treatment until the 6 h observations had been completed.

Venous reflex response (VRR)

The VRR is defined as the rise in intravenous pressure (measured in cm saline) which occurs distal to an occluding cuff following completion of deep expiration (occluded limb technique). The VRR was measured as previously described (Schapel & Betts, 1981). A superficial vein on the dorsum of the hand was cannulated with a 21-gauge Butterfly needle which was intermittently flushed with saline. Intraluminal pressure was transmitted via a saline-filled plastic tube (Portex) to a venous strain-gauge transducer (type PDCR75, Ormed Engineering Ltd, UK) connected to a Devices MX2 chart recorder using a paper speed of 0.25 mm s⁻¹.

The transducer system was calibrated after each measurement, using a saline-filled column. With the subject supine, the hand and forearm were supported on a padded rest, such that the hand and pressure transducer diaphragm were

level with the anterior axillary line. The circulation to the hand was temporarily arrested by rapid inflation of an 8 cm wide wrist cuff to 260 mm Hg. Free pressure transmission was then confirmed by lightly tapping the skin over the vein immediately proximal to the location of the needle point and producing a rapid, large-amplitude deflection on the chart paper.

When the venous pressure trace had stabilised, the subject was requested to inhale maximally and to exhale completely within 10 s, but not to hold his breath at either extreme. The maximum rise in venous pressure obtained represented the VRR.

Statistical analysis

A two-factor (subjects, treatment) analysis of variance with time as the repeated measure was used.

Results

Supine blood pressure (Figure 1)

There was a significant reduction in both systolic ($P < 0.01$) and diastolic ($P < 0.01$) blood pressure over the 6 h after alfuzosin in comparison with placebo. The peak effect on systolic blood pressure was at 3–4 h after the dose.

Figure 2 Mean supine heart rate before (time 0) and after treatment with alfuzosin (●) and placebo (■).

Supine heart rate (Figure 2)

Heart rate over the 6 h following treatment was significantly higher after alfuzosin in comparison with placebo ($P < 0.001$).

Venous reflex responses (Figure 3, and Table 1)

There was definite inhibition of VRR after alfuzosin treatment compared with placebo ($P < 0.001$). This was present 1 h after the dose and still evident at 6 h. Thus the effect on the VRR appeared to last longer than the effects on blood pressure or heart rate.

Discussion

Provided that a constant ambient temperature is maintained and excluding any significant external stimuli, the VRR can be used to study changes in peripheral venous tone produced by alterations in noradrenergic sympathetic nervous system activity. This technique offers a convenient, sensitive, reproducible and quantitative method for analysing sympathetically-mediated drug effects on the venous system. This study has demonstrated a highly significant reduction in the VRR in a group of healthy volunteers following a single oral 5 mg dose of alfuzosin in comparison with placebo. The inhibition of the VRR was strikingly evident at 1 h after the dose and persisted until the end of the experiment (6 h

Figure 3 Two venous reflex responses (VRR) from an individual subject.

Table 1 Venous reflex response (mean $\pm$ s.d.; cm saline) immediately before treatment (time 0) and at 20 min intervals thereafter to 6 h

Time		Alfuzosin 5 mg	Placebo
(h)	(min)		
0		13.1 (10.8)	10.2 (5.7)
	20	7.7 (7.3)	8.0 (6.4)
	40	7.3 (8.8)	7.7 (5.8)
1		4.1 (3.5)	8.8 (6.3)
	20	4.0 (5.0)	8.8 (8.8)
	40	3.6 (2.9)	8.9 (7.8)
2		4.5 (5.5)	11.0 (11.1)
	20	5.2 (5.5)	8.3 (6.1)
	40	4.2 (3.1)	7.0 (5.9)
3		2.9 (4.0)	7.7 (7.0)
	20	3.0 (3.3)	6.5 (5.9)
	40	3.3 (3.9)	9.4 (8.3)
4		4.8 (6.6)	8.6 (3.9)
	20	4.6 (7.1)	8.8 (5.4)
	40	6.0 (9.3)	8.0 (6.8)
5		4.8 (8.1)	8.3 (6.0)
	20	2.9 (3.5)	10.2 (8.7)
	40	3.9 (4.8)	8.0 (5.7)
6		4.0 (3.7)	8.7 (6.8)

post-dose). This effect on the VRR was probably mediated via alfuzosin's antagonism of nor-adrenaline at post-junctional α_1 -adrenoceptors. A direct venodilator action of alfuzosin could conceivably produce similar effects on VRR, but there is no evidence that the drug has any such pharmacological property.

References

- Epstein, G. T., Stampfer, M. & Beiser, G. D. (1968). Role of the capacitance and resistance vessels in vasovagal syncope. *Circulation*, **37**, 524-533.
- Jauering, R. A., Moulds, R. F. W. & Shaw, J. (1978). The action of prazosin in human vascular preparations. *Arch. int. Pharmacodyn.*, **231**, 81-89.
- Muller-Rucholtz, E. R., Grund, E., Hauer, F. & Lapp, E. R. (1979). Effect of carotid pressoreceptor stimulation on integrated systemic venous bed. *Basic Res. Cardiol.*, **74**, 467-476.
- Samueloff, S. L., Bevegard, B. S. & Shepherd, J. T. (1966). Temporary arrest of the circulation to a limb for the study of venomotor reactions in man. *J. appl. Physiol.*, **21**, 341-346.
- Schapel, G. T. & Betts, W. H. (1981). The effect of a single oral dose of prazosin on venous reflex response, blood pressure and pulse rate in normal volunteers. *Br. J. clin. Pharmacol.*, **12**, 873-881.
- Shepherd, J. T. & Vanhoutte, P. M. (1978). Role of the venous system in circulatory control. *Mayo Clin. Proc.*, **53**, 247-255.
- Walter, I. E., Khandelwal, J., Falkner, F. & Nies, A. S. (1975). The relationship of plasma guanethidine levels to adrenergic blockade. *Clin. Pharmacol. Ther.*, **18**, 571-580.

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The inhibition of the VRR in our study is comparable with that obtained in a previously published study using prazosin 500 μ g, in which every subject suffered from postural hypotension (Schapel & Betts, 1981). Suppression of the VRR in this latter study preceded the development of the postural fall in blood pressure. These workers suggested that such profound inhibition of the VRR might be predictive of the occurrence of the so called 'first-dose phenomenon' (Jauering *et al.*, 1978) linked to treatment with prazosin. Unfortunately, we did not measure standing blood pressure but we observed similarly profound inhibition of VRR following a 5 mg dose of alfuzosin. In our study, only modest effects of the drug on blood pressure and heart rate were seen, but these measurements were carried out in the supine position; no recordings were made in the standing position because we felt that repeated changes in posture might corrupt the VRR measurements. The inhibition of the VRR preceded the reflex tachycardia, an observation previously demonstrated (Schapel & Betts, 1981).

The VRR tended to fall during the 6 h following placebo and the results showed substantial variability, but a statistically significant difference between treatments was shown. Although Schapel & Betts (1981) felt that placebo comparison was not essential, our experience in this study suggests that a placebo treatment should always be included in the assessment of drug effects on VRR.

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