J. Pharm. Pharmacol. 1996, 48: 526–528
Received April 7, 1995
Accepted May 2, 1995

© 1996 J. Pharm. Pharmacol.

Circadian Variation of α_1-Adrenoceptor-mediated Pressor Response to Phenylephrine in Man

TONY C. K. THAM, SUZANNE GUY, JAMES G. RIDDELL, ROBIN G. SHANKS AND DEAN W. G. HARRON*

Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Northern Ireland

Abstract

The variability in the pressor effects of the α_1-adrenoceptor agonist phenylephrine was observed under placebo conditions in ten healthy subjects in a double blind randomized study. Phenylephrine infusions were administered before administration of placebo (baseline) and 2, 4, 8, 12, 24 and 48 h later.

The doses of phenylephrine required to increase systolic blood pressure by 20 mmHg after 8 and 12 h (5.30 and 9.30 pm, $81{\cdot}4 \pm 15{\cdot}3$ and $71{\cdot}1 \pm 16{\cdot}0$ $\mu g\ min^{-1}$, respectively) were significantly ($P < 0{\cdot}01$) less than the baseline values (8.30 am, $108{\cdot}0 \pm 27{\cdot}6$ g min^{-1}).

These results might indicate a circadian variation in the phenylephrine-induced α-adrenoceptor-mediated vascular response in healthy subjects. These observations lend further insight into circadian variations of vascular tone that might contribute to circadian rhythms in cardiovascular disease.

Circadian rhythms are prominent and reproducible temporal patterns that occur regularly over a 24 h period and have been described in a variety of physiological and pathological events, including heart rate and blood pressure (Bock & Kreuzenbeck 1966). There is an increased frequency of myocardial ischaemia (Mulcahy et al 1988), myocardial infarction (Muller et al 1985), sudden cardiac death (Muller et al 1987) and stroke (Marler et al 1989) during the early morning hours.

Although an understanding of circadian vascular responses might contribute towards explanation of circadian variation in cardiovascular events, there is little information on the circadian variation of α-adrenoceptor-mediated vascular responses in man. Although Panza et al (1991) demonstrated increased vascular tone during the morning as a result, either partly or entirely, of increased α-sympathetic activity, the study was not double blind; the response to an α-adrenoceptor agonist has not yet been determined. The present double blind randomized study evaluated the temporal variation in the pressor response to the α_1-adrenoceptor agonist phenylephrine under placebo control conditions.

Methods

The study was approved by the Research Ethics Committee of the Queen's University of Belfast. Ten healthy male volunteers (age 22 ± 2 y, mean weight $72{\cdot}3 \pm 7{\cdot}2$ kg) participated in the study after giving full written consent.

In order to prevent bias, the subjects underwent four identical studies on different days, each separated by a week, in which, after the first baseline infusion of phenylephrine, they received, in a double blind randomized manner, either placebo or three single oral doses of abanoquil, an α_1-adrenoceptor antagonist. This paper gives results for the placebo group only.

Having abstained from caffeine for at least 8 h, and after a light breakfast, the subjects presented themselves at 8.00 am at weekly intervals to a temperature-controlled (22–25°C) laboratory. An intravenous infusion of saline was commenced into a forearm vein. After resting supine for 15 min, baseline measurements of heart rate (five consecutive R-R intervals on an ECG rhythm strip) and blood pressure (Hawksley random zero sphygmomanometer; diastolic blood pressure was taken at Korotkoff phase 4) were made as a mean of two observations. At about 8.30 am, phenylephrine hydrochloride, 40 $\mu g\ min^{-1}$, was infused using an infusion pump (B Braun Perfusor VI). When the initial dose of phenylephrine 0·5 $\mu g\ min^{-1}$ had been running for 4 min, heart rate and blood pressure were again measured. After running for 8 min, the rate of infusion of phenylephrine was increased to 60 $\mu g\ min^{-1}$ and 4 min later, the same observations were repeated and the infusion increased after 8 min. The rate of infusion was increased gradually instead of being doubled in order to prevent an excessively rapid rise in blood pressure. Serial doses of phenylephrine through the range 40, 60, 100, 150, 200, 300, 400, 600, 1000 and 1500 $\mu g\ min^{-1}$ were infused in the same manner until the systolic blood pressure increased by 30 mmHg from baseline or the diastolic blood pressure exceeded 110 mmHg or the subject could not tolerate the effects of phenylephrine. Phenylephrine infusions were then performed at 2, 4, 8, 12, 24 and 48 h after the first observations. Supine heart rate and blood pressure were measured after a 15-min rest before each set of phenylephrine infusions.

For each subject, individual dose-response curves for the changes induced by phenylephrine with placebo were analysed by a non-linear quadratic fit (non-linear regression program of SPSS-PC (V3.0)). From the individual quadratic equation, the doses of phenylephrine required to increase systolic and diastolic blood pressure by 20 mmHg (PS20 and PD20, respectively) and to reduce heart rate by 15 beats min^{-1} (CD15) were calculated.

PS20, PD20 and CD15 at each time point for placebo were analysed by repeated measures analysis of variance (MANOVA program of SPSS-X (V2.0)) followed by Dunnett's test for multiple means comparison, comparing each time point with the baseline. A P-value of less than 0·05 was taken as

*Present address and correspondence: D. W. G. Harron, Department of Pharmacology, Faculty of Medicine, U.A.E. University, P. O. Box 17666, Al Ain, United Arab Emirates.

statistically significant. Results are expressed as means ± standard deviation.

Results

All ten subjects completed the study without any untoward effects. The mean inter-subject variability of PS20 ranged from 92·4 to 173·3 $\mu g\ min^{-1}$ and the day-to-day variability ranged from 108·0 to 127·8 $\mu g\ min^{-1}$.

The PS20 for placebo at 8 and 12 h (1730 and 2130 h; 81·4 ± 15·3 and 71·1 ± 16·0 $\mu g\ min^{-1}$, respectively) were significantly ($P < 0·01$) lower than at baseline (0830 h; 108·0 ± 27·6 $\mu g\ min^{-1}$). The PS20 at 24 and 48 h (8.30 am) did not differ from the baseline (Table 1, Fig. 1).

There was a trend for PD20 and CD15 to be lower at 8 and 12 h but the values were not statistically significant because of larger variability than for PS20. There were no changes in resting blood pressure or heart rate during the period (Table 1).

Discussion

Phenylephrine is an α_1-adrenoceptor agonist which produces peripheral vasoconstriction and increases systolic and diastolic blood pressure with a reflex decrease in heart rate (Depew 1988). This study observed greater sensitivity to phenylephrine in the evening than in the morning in healthy volunteers under placebo conditions, although the resting heart rates and blood pressures remained unchanged throughout the day. This suggests that the difference in the vascular responses did not result from a change in baseline haemodynamics. The phenylephrine-induced pressor response was reproducible, as the PS20 value was unchanged at the same time of the morning on three consecutive days (baseline, 24 and 48 h). The PD20 and CD15 responses were more variable than the PS20 and hence, although there was a trend for a similar increased response in the evening, the result was not statistically significant. These findings imply increased sensitivity to α-adrenoceptor agonists in the evening.

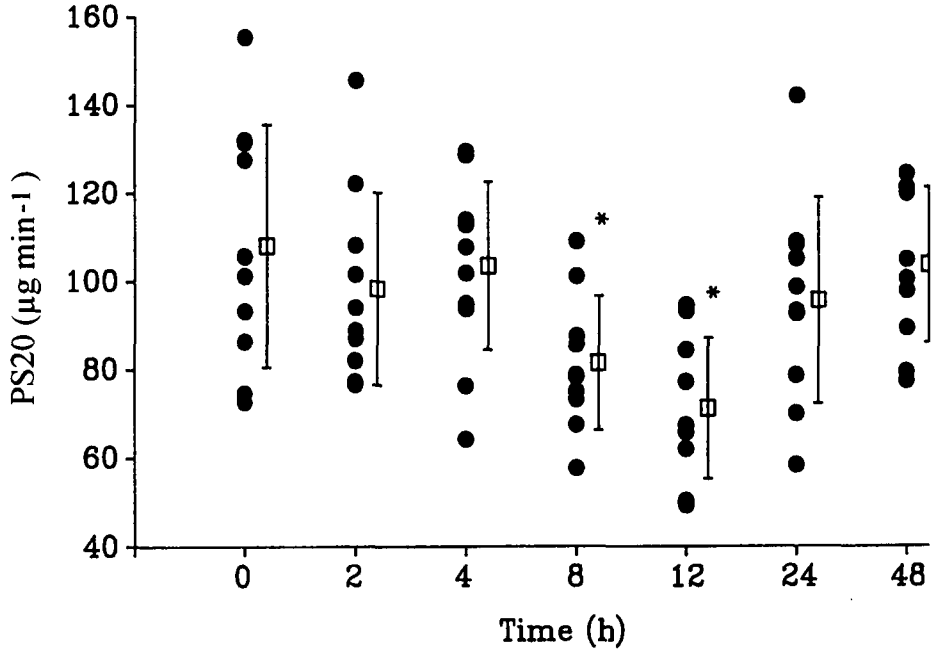

FIG. 1. Mean (± s.d.) infusion rate of phenylephrine ($\mu g\ min^{-1}$) required to increase systolic blood pressure by 20 mmHg (PS20) before and after administration of placebo in ten subjects. *$P < 0·01$ compared with baseline. ● Individual values; □ mean ± s.d.

Table 1. Mean (± s.d.) infusion rates of phenylephrine ($\mu g\ min^{-1}$) required to raise systolic and diastolic blood pressure by 20 mmHg (PS20 and PD20), reduce heart rate by 15 beats min^{-1} (CD15), resting systolic and diastolic blood pressure (mmHg) and heart rate (beats min^{-1}) before and after administration of placebo in ten subjects (except CD15 where n = 7).

Time (h)	PS20	PD20	CD15	Systolic (mmHg)	Diastolic (mmHg)	Heart rate (beats min^{-1})
0	108·0 ± 27·6	108·6 ± 29·2	100·1 ± 36·6	110·0 ± 9·3	67·9 ± 8·7	62·2 ± 4·1
2	98·3 ± 21·9	110·0 ± 41·9	78·5 ± 25·9	108·2 ± 10·6	71·6 ± 9·3	56·3 ± 6·7
4	103·5 ± 19·2	112·5 ± 36·2	100·0 ± 68·6	107·3 ± 9·7	69·2 ± 7·6	59·2 ± 7·8
8	81·4 ± 15·3*	101·1 ± 43·8	88·9 ± 26·9	106·9 ± 9·8	67·0 ± 6·3	57·6 ± 6·0
12	71·1 ± 16·0*	78·7 ± 15·4	67·9 ± 22·3	109·5 ± 10·7	68·2 ± 6·0	61·0 ± 8·0
24	95·6 ± 23·5	94·9 ± 25·3	103·0 ± 43·0	111·3 ± 9·2	68·4 ± 7·7	61·5 ± 8·6
48	103·7 ± 17·8	107·3 ± 16·0	72·9 ± 31·2	112·4 ± 6·0	70·6 ± 7·1	64·5 ± 6·7

*$P < 0·01$ compared with baseline.

The observations in this study suggest that circadian variability influences α-adrenoceptor-mediated vascular responses in man. In a recent study Panza et al (1991) demonstrated that in normal subjects forearm vascular resistance as determined by plethysmography was higher in the morning than at other times of the day. They then determined that the increase in resistance was a result of α-adrenergic activity because it was eliminated by intra-arterial infusion of phentolamine, an α-adrenoceptor antagonist. Our data are consistent with their findings. The increased resistance to phenylephrine in the morning could be explained by a high basal α-adrenoceptor-mediated sympathetic vasoconstriction in the morning, as found by Panza et al (1991). Thus our data support the suggestion that there is increased basal α-adrenergic activity in the morning which also results in increased vascular resistance.

Increased α-adrenergic vasoconstrictor activity has been demonstrated in cardiovascular conditions such as hypertension (Amann et al 1981), coronary stenosis (Brown et al 1984) and angina (Collins & Sheridan 1985) which show a circadian rhythm, with worsening in the morning. Our findings of a circadian variation in the α-adrenoceptor-mediated pressor response might be important in elucidating the pathogenesis of circadian rhythms in cardiovascular disease.

It is suggested that there might be a circadian variation in baroreflex sensitivity as it increases during sleep and decreases with mental arousal after waking (Conway et al 1983). As baroreflex sensitivity has been shown to be inversely related to phenylephrine pressor response (Conway et al 1984), it is possible that the circadian variation of the phenylephrine pressor response might be linked to this.

In conclusion, this study suggests that there is a circadian variation in phenylephrine-induced α-adrenoceptor-mediated vascular response with an increased sensitivity in the evening compared with morning. Our findings provide further insight into circadian variations of α-adrenergic influences that directly modulate vascular tone and which might therefore account, at least in part, for some of the circadian rhythms in cardiovascular disease. These observations would, in addition, be an important consideration in the design of studies evaluating the activities of α-antagonists by their effects on a phenylephrine-induced pressor response, as it would be important to compare their effects at the same time of the day to offset this variability.

References

Amann, F. W., Bolli, P., Kiowski, W., Buhler, F. R. (1981) Enhanced α-adrenoceptor-mediated vasoconstriction in essential hypertension. Hypertension 3 (Suppl. 1): I-119–I-123

Bock, K. D., Kreuzenbeck, W. (1966) Spontaneous blood-pressure variations in hypertension: the effect of antihypertensive therapy and correlations with the incidence of complications. In: Gross, F. (ed.) Antihypertensive Therapy: Principles and Practice: An International Symposium. Springer, New York, pp 224–241

Brown, B. G., Lee, A. B., Bolson, E. L., Dodge, H. T. (1984) Reflex constriction of significant coronary stenosis as a mechanism contributing to ischaemic left ventricular dysfunction during isometric exercise. Circulation 70: 18–24

Collins, P., Sheridan, D. (1985) Improvement in angina pectoris with α-adrenoceptor blockade. Br. Heart J. 53: 488–492

Conway, J., Boon, N., Jones, J. V., Sleight, P. (1983) Involvement of the baroreceptor reflexes in the changes in blood pressure with sleep and mental arousal. Hypertension 5: 746–748

Conway, J., Boon, N., Davies, C., Jones, J. V., Sleight, P. (1984) Neural and humoral mechanism involved in blood pressure variability. J. Hypertens. 2: 203–208

Depew, C. C. (1988) Intensive care therapeutics. In: Young, L. Y., Koda-Kimble, M. A. (eds) Applied Therapeutics: The Clinical Use of Drugs. 4th edn, Applied Therapeutics Inc., Vancouver, p 323

Marler, J. R., Price, T. R., Clark, G. L., Muller, J. E., Robertson, T., Mohr, J. P., Hier, D. B., Wolf, P. A., Caplan, A. R., Fowlkes, M. A. (1989) Morning increase in onset of ischaemic stroke. Stroke 20: 171–184

Mulcahy, D., Keegan, J., Cunningham, D., Quyyum, J., Crean, P., Park, A., Wright, C., Fox, K. (1988) Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. Lancet 2: 755–759

Muller, J. E., Stone, P. H., Turi, Z. G., Rutherford, J. P., Czeisler, C. A., Parker, C., Poole, W. K., Passamani, E., Roberts, R., Robertson, T., Sobel, B. E., Willerson, J. T., Braunwald, E. (1985) Circadian variation in the frequency of onset of acute myocardial infarction. N. Engl. J. Med. 313: 1315–1322

Muller, J. E., Ludmer, P. L., Willich, S. N., Tofler, G. H., Aylmer, G., Klangas, I., Stone, P. M. (1987) Circadian variation in the frequency of sudden cardiac death. Circulation 75: 131–138

Panza, J. A., Epstein, S. E., Quyyumi, A. A. (1991) Circadian variation in vascular tone and its relation to α-sympathetic vasoconstrictor activity. N. Engl. J. Med. 325: 986–990