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The dose dependency of the α- and β-adrenoceptor antagonist activity of carvedilol in man

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1 The α- and β-adrenoceptor antagonist activity of carvedilol, a β-adrenoceptor antagonist with vasodilating properties, and labetalol were investigated in 10 healthy male subjects. They received infusions with serially increasing concentrations of isoprenaline and phenylephrine before and after single oral doses of carvedilol 6.25, 12.5 and 25 mg, labetalol 400 mg and placebo at weekly intervals in a double-blind randomised manner. An exercise step test was performed at the end of the infusions.

2 The dose of isoprenaline required to increase heart rate by 25 beats min^{-1} (I_{25}) and the dose of phenylephrine required to increase systolic and diastolic blood pressure by 20 mm Hg (PS_{20} and PD_{20}) were calculated using a quadratic fit to individual dose-response curves. Comparisons were made with placebo and $P < 0.05$ was considered significant.

3 The I_{25} was increased by carvedilol 25 mg and labetalol 400 mg ($P < 0.05$). The dose ratios at I_{25} were: carvedilol 6.25 mg 2.1 ± 1.6, carvedilol 12.5 mg 3.1 ± 1.9, carvedilol 25 mg 6.4 ± 4.9 and labetalol 400 mg 8.8 ± 4.4.

4 The PS_{20} was increased by labetalol 400 mg ($P < 0.05$). The dose ratios at PS_{20} were: carvedilol 6.25 mg 1.0 ± 0.2; 12.5 mg, 1.2 ± 0.2; 25 mg, 1.3 ± 0.4 and labetalol 400 mg 2.2 ± 0.8.

5 The PD_{20} was increased by labetalol 400 mg ($P < 0.05$). The dose ratios at PD_{20} were: carvedilol 6.25 mg 1.1 ± 0.3; 12.5 mg, 1.3 ± 0.3; carvedilol 25 mg 1.3 ± 0.4 and labetalol 400 mg 2.1 ± 0.8.

6 Exercise heart rate was reduced by carvedilol 6.25, 12.5 and 25 mg and labetalol 400 mg (152.9 ± 13.4, 151.4 ± 9.0, 144.1 ± 10.5, 144.8 ± 11.0 beats min^{-1} respectively *vs* 161.8 ± 14.1 beats min^{-1} after placebo; $P < 0.05$).

7 In conclusion, carvedilol 6.25, 12.5 and 25 mg demonstrated β-adrenoceptor antagonist activity with some evidence for α-adrenoceptor antagonist activity with the 25 mg dose. Labetalol 400 mg showed both β- and α-adrenoceptor antagonist activity with a β– to α-adrenoceptor antagonist ratio of approximately 4 to 1.

Keywords α-adrenoceptor antagonism β-adrenoceptor antagonism carvedilol dose dependency

Introduction

Carvedilol combines the pharmacological effects of β-adrenoceptor antagonism and vasodilatation in one molecule [1].

The vasodilatation of carvedilol in man is thought to be mediated primarily by α-adrenoceptor antagonism because carvedilol 15 mg administered intravenously antagonised the pressor response to phenylephrine [2]. As the bioavailability of carvedilol is 24% [3], this intravenous dose is approximately equivalent to an oral dose of 60 mg. Oral doses of carvedilol 50 and 100 mg antagonised the phenylephrine systolic pressor response indicating that these

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doses possessed α-adrenoceptor antagonism [4]. However, the α-adrenoceptor antagonist activity of lower oral doses has not been studied.

The standard methods for demonstrating β-adrenoceptor antagonist activity in man are 1) to study the effect of the drug in antagonising the rise in heart rate caused by a β-adrenoceptor agonist like isoprenaline with the dose ratio at the I_{25} giving an indication of β-adrenoceptor antagonism; 2) the reduction in exercise tachycardia induced by the drug gives an indication of β-adrenoceptor antagonism [5].

The objectives of the study were to establish the β-adrenoceptor antagonist activity of oral doses of carvedilol 6.25, 12.5 and 25 mg by their effect on isoprenaline-induced tachycardia and exercise heart rate and also to establish whether α-adrenoceptor antagonism occurs at these doses by their effect on the pressor response to phenylephrine. These effects were compared with labetalol 400 mg which has approximately equivalent β-adrenoceptor antagonist activity to carvedilol 25 mg [4].

Methods

Ten healthy male volunteers (age 23 ± 4 years, mean weight 74.0 ± 9.4 kg) participated in the study after full informed consent. The study was approved by the Queen's University Ethics Committee. After a light breakfast, having abstained from caffeine for at least 8 h, the subjects presented at the same time on each study day and an intravenous infusion of saline was commenced into a forearm vein. After resting supine for 30 min, baseline measurements of heart rate (five consecutive R-R intervals on a direct writing electrocardiogram) and blood pressure as a mean of two observations (Hawksley random zero sphygmomanometer; 4th Korotkoff sound) were made. Phenylephrine hydrochloride 40 μg min^{-1} was then infused using an infusion pump (B. Braun Perfusor VI). After the initial dose of phenylephine 40 μg min^{-1} had been running for 4 min, heart rate and blood pressure were measured. After running for 8 min, the rate of infusion of phenylephrine was then increased to 60 μg min^{-1} and after 4 min, the same observations were repeated and the infusion increased. Serial rates of infusions of phenylephrine through the range 40, 60, 100, 150, 200, 300, 400, 60, 1000 μg min^{-1} were infused in the same manner until the systolic blood pressure increased by 30 mm Hg from baseline or the diastolic blood pressure exceeded 110 mm Hg or the subject could not tolerate the effects of phenylephrine.

After the last infusion of phenylephrine there was a 10 min rest to allow the heart rate and blood pressure to return to baseline values after which further baseline observations of heart rate and blood pressure were made. Isoprenaline sulphate 0.5 μg min^{-1} with sodium metabisulphite 0.1% as preservative was then infused using a Braun Perfusor pump. The infusion was stopped when the heart rate increased by 50 beats min^{-1} from baseline or the systolic blood pressure increased by more than 30 mm Hg or the subject could not tolerate the effects of isoprenaline. The order of the series of phenylephrine and isoprenaline infusions was randomised.

Subjects then received a single oral dose of carvedilol 6.25, 12.5 and 25 mg, labetalol 400 mg or placebo on each study day at weekly intervals in a double-blind randomised manner until each subject received all the treatments. Each subject received carvedilol 12.5 mg prior to receiving carvedilol 25 mg to prevent postural effects from receiving the higher dose first. Two hours after the treatment, measurements were made of the response of heart rate and blood pressure to serial infusions of phenylephrine and isoprenaline in the same manner as described. The order in which the series of infusions was carried out was randomised. After the last infusion of phenylephrine or isoprenaline and after a 30 min rest period, the subject performed a standard exercise step test by stepping on and off a box 46 cm high at a rate of 32 steps min^{-1} for 3 min. Heart rate was measured within 5 s of completing the exercise from the first five consecutive R-R intervals on an electrocardiogram.

For each post-drug and pre-drug treatment in every subject, individual dose-response curves for the changes induced by isoprenaline and phenylephrine were analysed by a non-linear quadratic fit (non-linear regression programme of SPSS-PC (Statistical Package for Social Sciences) (V3.0)). From the individual quadratic equation, the following indices were calculated: the dose of isoprenaline required to increase heart rate by 25 beats min^{-1} (I_{25}), the dose of phenylephrine required to increase systolic blood pressure by 20 mm Hg (PS_{20}) and the dose of phenylephrine required to increase diastolic blood pressure by 20 mm Hg (PD_{20}). Dose ratios at these doses were calculated.

I_{25}, PS_{20}, PD_{20} and exercise heart rate were analysed by repeated measures analysis of variance (MANOVA Programme of SPSS-X (V2.0)) followed by Dunnett's test for multiple means comparison, comparing treatments with placebo [6]. A P value of less than 0.05 was taken as statistically significant. Results are expressed as means ± s.d.

Results

Before treatment there was no difference in the I_{25}, PS_{20} or PD_{20} on different days. There was no order effect of the infusions on the I_{25}, PS_{20} or PD_{20}.

The dose-response curve for isoprenaline induced tachycardia for one subject could not be analysed as he did not achieve the required rise in heart rate although his systolic blood pressure increased by more than 30 mm Hg; therefore he was excluded from the analysis of the I_{25}.

The doses for isoprenaline to increase systolic blood pressure and decrease diastolic blood pressure and for phenylephrine to decrease heart rate were not analysed statistically because in several cases, the

values did not reach the steep part of the dose-response curve.

Power calculations showed that in order to detect a difference with 90% probability at a P level of 0.05 with 10 subjects, the difference in the I_{25} had to be 40–50%, PS_{20} 30–40% and PD_{20} 40–50%.

Isoprenaline and heart rate (Table 1, Figure 1)

The mean I_{25} for carvedilol 25 mg (10.1 (95% CI 6.2–14.0) μg min^{-1}) and labetalol 400 mg (15.6 (9.8–21.4) μg min^{-1}) was significantly greater than placebo (2.0 (1.2–2.8) μg min^{-1}) ($P < 0.05$). There was a trend towards an increase in the I_{25} with carvedilol 6.25 and 12.5 mg but this did not reach statistical significance.

The dose ratios at I_{25} were: carvedilol 6.25 mg 2.1 ± 1.6, carvedilol 12.5 mg 3.1 ± 1.9, carvedilol 25 mg 6.4 ± 4.9 and labetalol 400 mg 8.8 ± 4.4.

Phenylephrine and systolic blood pressure (Table 1)

The mean PS_{20} for labetalol 400 mg (199.6 (149.6–249.5) μg min^{-1}) was significantly greater than placebo (93.6 (74.2–113.1) μg min^{-1}) ($P < 0.05$). There was a trend towards an increase in the PS_{20} with carvedilol 25 mg (121.6 (90.8–152.5) μg min^{-1}) but this did not reach statistical significance. Carvedilol 6.25 mg (94.2 (79.0–109.3) μg min^{-1}) and 12.5 mg (114.4 (92.4–136.4) μg min^{-1}) did not change the PS_{20}.

The dose ratios at PS_{20} were: carvedilol 6.25 mg 1.0 ± 0.2, carvedilol 12.5 mg 1.2 ± 0.2, carvedilol 25 mg 1.3 ± 0.4 and labetalol 400 mg 2.2 ± 0.8.

Phenylephrine and diastolic blood pressure (Table 1)

The mean PD_{20} for labetalol 400 mg (191.0 (144.9–237.2) μg min^{-1}) was significantly greater than

Table 1 Doses of isoprenaline required to increase heart rate by 25 beats min^{-1} (I_{25}), doses of phenylephrine required to raise systolic blood pressure by 20 mm Hg (PS_{20}) and diastolic blood pressure by 20 mm Hg (PD_{20}) (95% confidence intervals are in brackets)

	I_{25} (n = 9)		PS_{20} (n = 10)		PD_{20} (n = 10)	
	Pre-drug (μg min^{-1})	*Post-drug* (μg min^{-1})	*Pre-drug* (μg min^{-1})	*Post-drug* (μg min^{-1})	*Pre-drug* (μg min^{-1})	*Post-drug* (μg min^{-1})
Carvedilol 6.25 mg	1.6 (1.2–2.0)	3.4 (2.1–4.6)	109.7 (95.5–124.0)	94.2 (79.0–109.3)	101.3 (80.9–121.7)	98.9 (74.9–122.8)
Carvedilol 12.5 mg	1.7 (1.4–2.0)	5.1 (4.0–6.0)	113.4 (89.6–137.4)	114.4 (92.4–136.4)	130.5 (91.4–169.6)	121.2 (94.5–148.0)
Carvedilol 25 mg	1.9 (1.4–2.4)	10.1 (6.2–14.0)*	110.5 (90.9–130.0)	121.6 (90.81–152.5)	124.7 (91.7–157.8)	118.6 (90.2–147.0)
Labetalol 400 mg	1.6 (1.3–2.0)	15.6 (9.8–21.4)*	112.4 (97.4–127.4)	199.6 (149.6–249.5)*	111.0 (99.2–122.8)	191.0 (144.9–237.2)*
Placebo	1.7 (1.3–2.1)	2.0 (1.2–2.8)	111.8 (90.7–132.8)	93.6 (74.2–113.1)	124.2 (98.6–149.9)	95.7 (74.5–116.8)

*$P < 0.05$ compared with placebo.

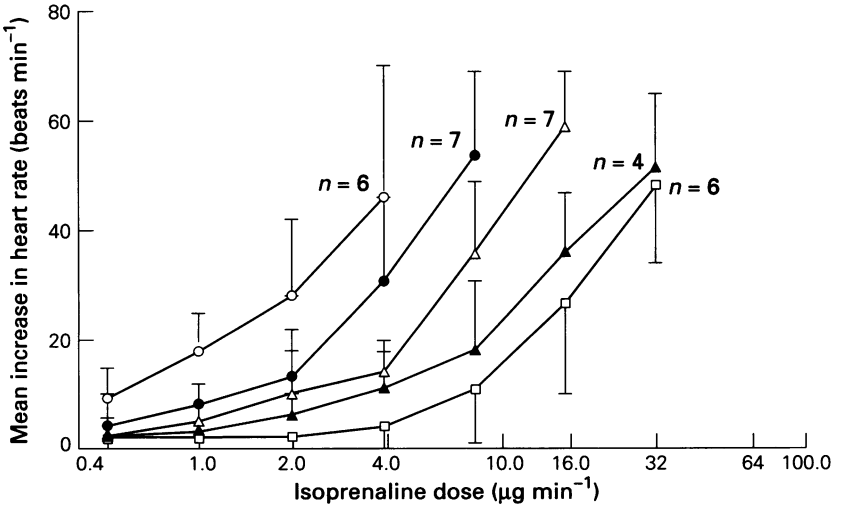

Figure 1 Mean increase in heart rate by serial infusions of increasing concentrations of isoprenaline after oral carvedilol 6.25 mg (●), 12.5 mg (△), 25 mg (▲), labetalol 400 mg (□) and placebo (○).

placebo (95.7 (74.5–116.8) μg min^{-1}) ($P < 0.05$). There was a trend for carvedilol 12.5 (121.2 (94.5–148.0) μg min^{-1}) and 25 mg (118.6 (90.2–147.0) μg min^{-1}) to increase the PD_{20} but these were not statistically significant. Carvedilol 6.25 (98.9 (74.9–122.8) μg min^{-1}) did not change the PD_{20}.

The dose ratios at PD_{20} were: carvedilol 6.25 mg 1.1 ± 0.3, carvedilol 12.5 mg 1.3 ± 0.3, carvedilol 25 mg 1.3 ± 0.4 and labetalol 400 mg 2.1 ± 0.8.

Exercise heart rate

Exercise heart rate was reduced by carvedilol 6.25, 12.5 and 25 mg and labetalol 400 mg compared with placebo (152.9 ± 13.4, 151.4 ± 9.0, 144.1 ± 10.5, 144.8 ± 11.0 and 161.8 ± 14.1 beats min^{-1} respectively; $P < 0.05$).

Discussion

Carvedilol 25 mg and labetalol 400 mg demonstrate β-adrenoceptor antagonism by increasing the I_{25} dose ratio and reducing exercise tachycardia. Carvedilol 6.25 and 12.5 mg also demonstrate a degree of β-adrenoceptor antagonism as they significantly reduced exercise tachycardia, although the tendency to shift the isoprenaline tachycardia dose-response curve to the right with dose ratios of 2.1 and 3.1 was not significant. The reduction in exercise tachycardia is more sensitive than the isoprenaline I_{25} dose ratio in detecting β-adrenoceptor antagonism due to a larger variability in isoprenaline responses than in the reduction in exercise tachycardia. Carvedilol 25 mg and labetalol 400 mg have approximately equivalent β-adrenoceptor antagonist activity as their dose ratios and reduction in exercise heart rate were similar. These results are consistent with a previous study where oral doses of 6.25 to 50 mg reduced exercise tachycardia [7]. These findings also support those of Tomlinson *et al.* [8] who demonstrated β-adrenoceptor antagonism by a reduction in exercise heart rate with oral doses from 12.5 mg.

The standard method for demonstrating α-adrenoceptor antagonist activity in man is to study the effect of the drug on the rise in blood pressure caused by an α-adrenoceptor agonist like phenylephrine with the dose ratio at the PS_{20} and PD_{20} giving an indication of α-adrenoceptor antagonism [9–11]. Only labetalol 400 mg demonstrated significant α-adrenoceptor antagonism but carvedilol 25 mg shows a trend to shift the phenylephrine systolic pressure dose-response curve to the right. The increase in the PS_{20} with carvedilol 25 mg was about 30% while the power of the study enabled a change of 30 to 40% to be detected. This suggests that carvedilol 25 mg might have demonstrated statistically significant α-adrenoceptor antagonist activity if more subjects had been used.

Although carvedilol 12.5 mg always preceded the 25 mg dose, only the efficiency (a measure of the precision of the comparison of two treatments relative to the precision when the design is optimal) of the comparison between these two treatments was affected. As this comparison was not made the power of the comparisons between the treatments and placebo is unaffected.

The evidence for the α-adrenoceptor antagonist activity of carvedilol in animals has been conflicting. In experiments on rat isolated aortic strips and pithed rats, the dose of carvedilol required for a specific inhibitory effect on noradrenaline responses was at least 20 times higher than that required for hypotension in spontaneously hypertensive rats and the α-adrenoceptor antagonist activity was at least 20 times lower than the β-adrenoceptor antagonist activity [12]. While carvedilol has been shown to relax the aortic strip in rat after it has been precontracted by noradrenaline it appears to be a non-specific effect as it is only to a similar degreee as glyceryl trinitrate and much less than that seen with prazosin [13]. Carvedilol shifted the pressor dose-response curve to α_1-adrenoceptor stimulation with methoxamine in the pithed rat but this was much less than that seen with phentolamine, using doses which had an equivalent antihypertensive effect [12]. In rabbit isolated aorta, carvedilol antagonises the vasoconstrictor response to noradrenaline [14]. Carvedilol antagonises the α-adrenoceptor mediated vasopressor response to cirazoline in the pithed rat [14].

There is some evidence for α-adrenoceptor antagonism in man. Cubeddu *et al.* [2] administered an intravenous dose of carvedilol 15 mg, which is approximately equivalent to 60 mg orally as bioavailability is 24% [3], to healthy volunteers and found that it inhibited the pressor effect of phenylephrine but did not affect angiotensin II pressor response. Tomlinson *et al.* [4] found that oral carvedilol 50 mg and 100 mg shifted the phenylephrine systolic pressure dose-response curve in healthy volunteers. In their study, carvedilol 50 mg produced a slight displacement of the angiotensin II systolic pressure dose-response curve which was similar to the hydralazine-propranolol combination but although neither of these reached significance this could be evidence for a direct vasodilating effect of carvedilol particularly at lower doses. They also found that carvedilol 50 and 100 mg demonstrated greater β-adrenoceptor antagonism than labetalol 400 mg which would be consistent with our finding that carvedilol 25 mg had equivalent β-adrenoceptor antagonism to labetalol 400 mg. A probable explanation of why we did not show a shift of the phenylephrine pressor response is that the lower doses of carvedilol used did not possess significant α-adrenoceptor antagonism thus indicating that a possible threshold for α-adrenoceptor antagonism is an oral dose of 25 mg. However in patients with hypertension, carvedilol 25 mg has been shown to demonstrate α-adrenoceptor antagonist activity by reducing the pressor response to phenylephrine [15]; this may simply reflect an increased sensitivity to carvedilol in hypertensive patients in contrast to healthy subjects.

The relative degrees of β- and α-adrenoceptor antagonism of any drug dose may be derived from the

ratio of the I_{25} to PS_{20} dose ratio (I_{25} dose ratio divided by PS_{20} dose ratio) [4, 16]. In this study, the ratio of β-adrenoceptor antagonism to α-adrenoceptor antagonism for labetalol 400 mg is approximately 4:1. This is consistent with the findings of Tomlinson *et al.* [4] who found a β- to α-adrenoceptor antagonism with labetalol at the same dose to be 4.9 to 1. Other studies have found the ratio of β- to α-adrenoceptor antagonism to be between 3:1 and 7:1 [17, 18]. The dose ratio for α-antagonism in labetalol 400 mg in this study was 2.2 which is similar to that described by Tomlinson *et al.* [4] which was 2.4. Assuming a significant α-antagonism for carvedilol 25 mg, its ratio for β- to α-adrenoceptor antagonism would be 5:1 which is slightly higher than that for labetalol 400 mg. Thus, carvedilol 25 mg may be expected to show α-adrenoceptor antagonism at oral doses greater than 25 mg.

In conclusion, carvedilol 6.25, 12.5 and 25 mg demonstrated dose dependent β-adrenoceptor antagonist activity. There was some evidence of α-adrenoceptor antagonist activity at the 25 mg dose. Laetalol 400 mg showed both β- and α-adrenoceptor antagonist activity with a β- to α-adrenoceptor antagonist ratio of approximately 4 to 1.

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References

1 Abshagen U. A new molecule with vasodilating and beta-adrenoceptor blocking properties. *J Cardiovasc Pharmacol* 1987; **10** (Suppl 11): S23–S32.

2 Cubeddu LX, Fuenmayor N, Varin F, Villagra VG, Colindres RE, Powell JR. Mechanism of the vasodilatory effect of carvedilol in normal volunteers: A comparison with labetalol. *J Cardiovasc Pharmacol* 1987; **10** (Suppl 11): S81–S84.

3 Neugebauer G, Akpan W, Mollendorf EV, Neubert P, Reiff K. Pharmacokinetics and disposition of carvedilol in humans. *J Cardiovasc Pharmacol* 1987; **10** (Suppl 11): S85–S88.

4 Tomlinson B, Bompart F, Graham BR, Liu JB, Prichard BNC. Vasodilating mechanism and response to physiological pressor stimuli of acute doses of carvedilol compared with labetalol, propranolol and hydralazine. *Drugs* 1988; **36**: 37–47.

5 McDevitt DG. The assessment of beta-adrenoceptor blocking drugs in man. *Br J Clin Pharmacol* 1977; **4**: 413–425.

6 Dunnett CW. New tables for multiple comparisons with a control. *Biometrics* 1964; **20**: 482–491.

7 Tham TCK. Studies of the dose dependency of the activity of some drugs acting at the alpha and beta adrenoceptors in man. *MD Thesis, Queen's University of Belfast* 1990; 4.1–4.20.

8 Tomlinson B, Cronin CJ, Graham BR, Prichard BNC. Haemodynamics of carvedilol in normal subjects compared with propranolol, pindolol, and labetalol. *J Cardiovasc Pharmacol* 1987; **10** (Suppl 11): S69–S75.

9 Sumner DJ, Elliott HL, Vincent J, Reid JL. A pragmatic approach to the pressor dose-response as an index of vascular reactivity and adrenoceptor function in man. *Br J Clin Pharmacol* 1987; **23**: 505–510.

10 Sumner DJ, Elliott HL. The pressor dose-response in clinical cardiovascular pharmacology. *Br J Clin Pharmacol* 1987; **23**: 499–503.

11 Sumner DJ, Elliott HL, Reid JL. Analysis of the pressor dose response. *Clin Pharmacol Ther* 1982; **32**: 450–458.

12 Sponer G, Strein K, Muller-Beckmann B, Bartsch W. Studies on the mode of vasodilating action of carvedilol. *J Cardiovasc Pharmacol* 1987; **10** (Suppl 11): S42–S48.

13 Strein K, Sponer G, Muller-Beckmann B, Bartsch W. Pharmacological profile of carvedilol, a compound with beta-blocking and vasodilating properties. *J Cardiovasc Pharmacol* 1987; **10** (Suppl 11): S33–S41.

14 Ruffolo RR, Gellai M, Hieble JP, Willette RN, Nichols AJ. The pharmacology of carvedilol. *Eur J Clin Pharmacol* 1990; **38**: S82–S88.

15 Giannattasio C, Cattaneo BM, Seravalle G, Carugo S, Mangoni AA, Grassi G, Zanchetti A, Mancia G. Alpha 1-blocking properties of carvedilol during acute and chronic administration. *J Cardiovasc Pharmacol* 1992; **19** (Suppl 1): S18–S22.

16 Richards DA, Prichard BNC. Clinical pharmacology of labetalol. *Br J Clin Pharmacol* 1979; **8**: 89S–93S.

17 Richards DA. Pharmacological effects of labetalol in man. *Br J Clin Pharmacol* 1976; **3** (Suppl): 721–723.

18 Richards DA, Prichard BNC, Boakes AJ, Tuckman J, Knight EJ. Pharmacological basis for antihypertensive effects of intravenous labetalol. *Br Heart J* 1977; **39**: 99–106.

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