Br. J. Pharmac. (1980), **70**, 287–293

DIRECT VASODILATATION BY LABETALOL IN ANAESTHETIZED DOGS

RICHARD C. DAGE & CHIH PENG HSIEH

Merrell Research Center, Merrell-National Laboratories,
Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

1 The effects of several doses of labetalol (0.03 to 1 mg/kg) given intravenously and into the vertebral artery were examined in anaesthetized dogs. Labetalol produced no immediate (5 min) change in blood pressure or heart rate when given by either route, with one exception. Heart rate increased after the first dose (0.03 mg/kg i.v.) of labetalol. By contrast, clonidine (1 μg/kg) elicited an immediate and prolonged fall in blood pressure and heart rate when given into the vertebral artery, but not intravenously.

2 In the isolated perfused gracilis muscle of the dog, following α- and β-adrenoceptor blockade, intra-arterial injections of labetalol (0.3 to 10 mg) or diazoxide (0.3 to 1 mg) produced decreases in perfusion pressure that were dose-related in both magnitude and duration. The doses of labetalol and diazoxide required to produce a half-maximal vasodilatation were 1.5 mg and 0.7 mg respectively.

3 In adrenalectomized, vagotomized spinal dogs, both labetalol (0.1 to 1 mg/kg i.v.) and hydralazine (1 mg/kg i.v.) elicited a fall in blood pressure without changing heart rate or cardiac output.

4 These results suggest that the hypotension produced by systemically administered labetalol does not involve an action in the brain. It may involve instead a direct vasodilatation of resistance blood vessels, since labetalol in sufficient amounts, directly dilates resistance vessels and lowers blood pressure in dogs devoid of adrenergic tone. Direct vasodilatation may be a component of the hypotensive action of labetalol.

Introduction

Labetalol has been reported to lower blood pressure in normotensive or hypertensive animals including man (Farmer, Kennedy, Levy & Marshall, 1972; Collier, Dawnay, Nacheu & Robinson, 1972; Brittain & Levy, 1976; Kane, Gregg & Richards, 1976). Its mode of action is not fully known but has been attributed to concomitant peripheral α- and β-adrenoceptor antagonism (Brittain & Levy, 1976; Edwards & Raferty, 1976; Koch, 1976; Brogden, Heel, Speight & Avery, 1978; Richards and Prichard, 1978). However, the hypotensive effectiveness of labetalol is greater than would be predicted from its α- and β-adrenoceptor blocking potency (Farmer *et al.*, 1972; Brittain & Levy, 1976; Dollery, 1976; Johnson, La Brooy & Munro-Faure, 1976; Brogden *et al.*, 1978) suggesting an additional action. The experiments described here were undertaken to discover whether labetalol had a central component or a direct vasodilator component that could contribute to its hypotensive action following systemic administration.

Method

In these experiments, blood pressure was recorded by means of arterial pressure transducers (Gould Statham, Model P23DC). All variables were recorded with a polygraph (Grass Instrument Co., Model 7B).

Comparison of the effects of labetalol and clonidine given into the femoral vein or into the vertebral artery

The technique employed was previously described by Constantine & McShane (1968). Five dogs (10 to 16 kg) of either sex were anaesthetized with α-chloralose (100 mg/kg i.v.). The right vertebral artery was exposed through an incision on the ventral aspect of the neck. The vertebral artery was identified as the first branch of the subclavian artery. A 25-gauge needle attached to a suitable cannula was inserted rostrad into the vertebral artery for drug administration. Also, another cannula was inserted into the left femoral vein for drug administration. Arterial blood pressure was recorded from a cannula placed in the

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right femoral artery and connected to an arterial pressure transducer. To test the model, clonidine (1 μg/kg) was given to eight dogs, first into the femoral vein (i.v.) and then into the vertebral artery (i.a.). Successive doses of labetalol (0.03, 0.1, 0.3 and 1 mg/kg) were given to four dogs in identical fashion. In an additional dog, the low dose of labetalol was omitted and the routes of administration reversed (i.e., i.a. was followed by i.v.). Labetalol and clonidine were dissolved in 0.9% w/v NaCl solution (saline). Injection volumes varied with the dose and ranged from 0.03 to 1.2 ml. Each dose was infused at the rate of 1 ml/min. Saline alone, in the largest dose to be given, was injected at the beginning of each experiment and found not to produce an effect. Heart rate was recorded by counting the R-waves on the ECG (lead II).

Effects of labetalol and hydralazine in adrenalectomized, vagotomized spinal dogs

Four dogs (11 to 21 kg) of either sex were anaesthetized with pentobarbitone sodium (35 mg/kg i.v.). The spinal cord was sectioned between the first and second cervical vertebra following bilateral vagotomy and bilateral adrenalectomy. The animals were artificially respired with a positive pressure respirator. Cardiac output less coronary blood flow, subsequently referred to as cardiac output, was recorded with a flowmeter (Biotronex, BL610) by placing an electromagnetic flow transducer around the root of the ascending aorta. Heart rate was measured with a tachograph (Grass, Model 7P4D) triggered by the R-wave of the ECG. Arterial blood pressure was measured from the iliac artery by an arterial pressure transducer.

A period of thirty minutes was allowed for stabilization of blood pressure following the surgical preparation of each animal. Then, a constant intravenous infusion of angiotensinamide (0.025 μg kg^{-1} min^{-1}) was started to enhance vascular tone and support blood pressure. When blood pressure appeared stable for 10 min, three injections of labetalol (0.01, 0.1 and 1 mg/kg i.v.) were given 5 to 10 min apart. Hydralazine (1 mg/kg i.v.) was given at the end of the experiment. Labetalol and hydralazine were dissolved in saline or distilled water to make concentrations ranging from 0.1 to 1%. Drug injections were made into the inferior vena cava just rostrad of the iliac bifurcation without interrupting the angiotensin amide infusion. Injection volumes ranged from 0.11 to 2.1 ml. Each injection of drug was followed by 2 ml of saline, intravenously. It has been reported previously in anaesthetized dogs and confirmed in our laboratory (unpublished data) that labetalol does not affect the vasopressor responses to angiotensinamide (Farmer *et al.*, 1972).

Effects of labetalol and diazoxide in the perfused dog gracilis muscle

Eleven dogs (15 to 26 kg) of either sex were divided into the following two treatment groups: (1) labetalol ($n = 6$); (2) diazoxide ($n = 5$). The dogs were anaesthetized with pentobarbitone sodium (35 mg/kg i.v.). The left gracilis muscle was isolated, denervated and perfused with the dog's own blood. Denervation was performed by sectioning all nerves and blood vessels to the gracilis muscle. Arterial blood was pumped from the aorta into the gracilis artery with a pulsatile perfusion pump (Sigma Motor, Model TM 8). Blood flow was maintained constant throughout each experiment (15.23 ± 2.94 ml/min). Perfusion pressure was set at the beginning of each experiment to approximate systemic arterial blood pressure. The dogs were treated with heparin (6 mg/kg i.v.) before the start of the perfusion. To insure adrenoceptor blockade, dogs were pretreated with doses of propranolol hydrochloride (1 mg/kg i.v.) and phentolamine hydrochloride (10 to 15 mg/kg i.v.) that adequately blocked α- and β-adrenoceptors as judged by the nearly complete (>82%) inhibition of perfusion pressure responses to isoprenaline hydrochloride (1 μg base i.a.) or (−)-noradrenaline bitartrate (1 μg base i.a.). Doses of 0.1, 0.3, 1, 3, and sometimes 10 mg of labetalol or diazoxide were injected into the perfusion circuit and changes in perfusion pressure measured. Measurements represent maximum changes in perfusion pressure. Perfusion pressure is a measure of vascular resistance since flow is constant. Perfusion pressure was allowed to return to baseline (90 to 100% recovery = complete recovery) following each dose of drug. At the end of each experiment, 10, 30 and 100 μg intra-arterially of nitroglycerine were given to assess the maximum vasodilatation and test doses of isoprenaline and of noradrenaline were repeated, to insure persistent adrenoceptor blockade. Perfusion pressure, systemic arterial blood pressure and heart rate were monitored continuously throughout the experiment.

All drugs were dissolved in saline. Each dose of drug was given in 0.1 ml of vehicle except for the 10 mg/kg dose of labetalol which was given in 0.2 ml of vehicle. Drug-induced changes in perfusion pressure (post-dose minus pre-dose) were corrected for any response elicited by vehicle (corrected value = drug response minus vehicle response).

Statistical analysis

The results are expressed as mean value (X) ± the standard error of the mean (s.e.). The data were analyzed either by a t test (Snedecor & Cochran, 1967) or a repeated measure analysis of variance (Winer, 1971). Statistical significance was taken at $P < 0.05$.

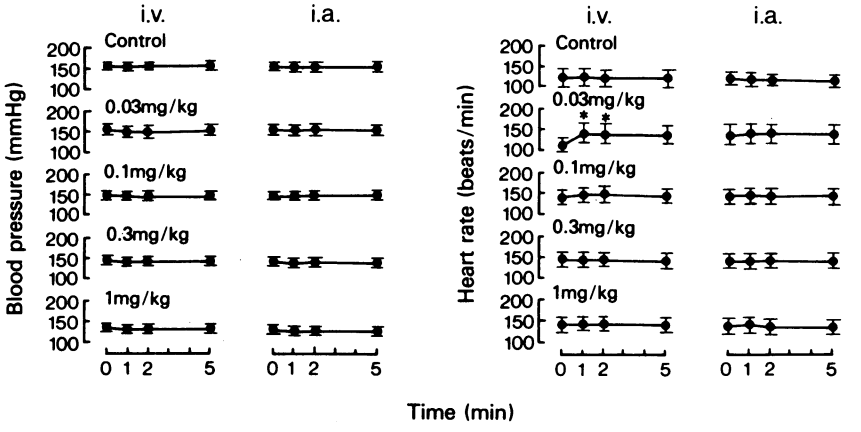

Figure 1 Blood pressure and heart rate in 5 anaesthetized dogs given labetalol (0.03, 0.1, 0.3 and 1 mg/kg) into the femoral vein (i.v.) and into the vertebral artery (i.a.). Successive doses were given 5 to 21 min apart alternately by each route. Only 4 dogs received the 0.03 mg/kg dose. Injections were given at time zero. Analysis of the data (*t* test) for differences in the effect of labetalol, i.v. vs i.a., revealed no significant differences with one exception. A significant increase in heart rate was observed following 0.03 mg/kg i.v. but not i.a. (asterisk indicates $P < 0.05$).

Results

Comparison of the effects of labetalol and clonidine given into the femoral vein or the vertebral artery

Labetalol (0.03 to 1 mg/kg) did not produce a significant change in blood pressure at any individual dose whether given into the femoral vein or the vertebral artery (Figure 1). Nevertheless, after a cumulative dose of 2.86 mg/kg of labetalol, blood pressure fell 25 ± 5 mm Hg (from 153 ± 13 mmHg) during the experiments, and this effect was significant ($P < 0.05$). Similarly, except for the intravenous 0.03 mg/kg dose, these same doses of labetalol did not elicit a significant change in heart rate (Figure 1). However, the 0.03 mg/kg intravenous dose produced a significant ($P < 0.05$) increase in heart rate 31 ± 11 beat/min; range 10–62 beats/min that remained elevated for the duration of the experiment. Subsequent doses produced little or no additional increase. By contrast, a low dose of the centrally acting hypotensive drug, clonidine (1 μg/kg) produced predominantly a rise in blood pressure (15 ± 2 mmHg from 148 ± 6 mmHg) and a transient (<3 min) bradycardia (−26 ± 4 beats/min from 109 ± 11 beats/min) when injected into the femoral vein, but a fall in blood pressure (−26 ± 4 mmHg from 145 ± 6 mmHg) and a prolonged (>30 min) bradycardia (−31 ± 4 beats/min from 103 ± 3 beats/min) when injected into the vertebral artery.

Effects of labetalol and hydralazine in adrenalectomized, vagotomized spinal dogs

Labetalol in intravenous doses of 0.1 and 1 mg/kg produced a fall in blood pressure in anaesthetized, adrenalectomized, vagotomized, spinal dogs (Figure 2). Such dogs are devoid of adrenergic tone. By contrast, heart rate and cardiac output did not change significantly after these doses of labetalol. However, if only the maximum changes in cardiac output were considered regardless of time, a small but significant ($P < 0.05$) increase (53 ± 8 ml/min) in cardiac output was seen with 0.01 mg/kg of labetalol and a small decrease with 1 mg/kg (however, not significant). Hydralazine (1 mg/kg i.v.), given at the end of each experiment, also produced a fall in blood pressure without significantly changing heart rate or cardiac output. Over the 35 min duration of this experiment, blood pressure fell with labetalol (1.11 mg/kg i.v., cumulative dose) −16 ± 2 mmHg, from 81 ± 8 mmHg (significant at $P < 0.001$), whereas heart rate and cardiac output did not change significantly (−7 ± 4 beats/min, from 128 ± 4 beats/min and 75 ± 79 ml/min) respectively.

Effects of labetalol and diazoxide in the perfused dog gracilis muscle

Systemic blood pressure, heart rate and gracilis muscle perfusion pressure, before administration of

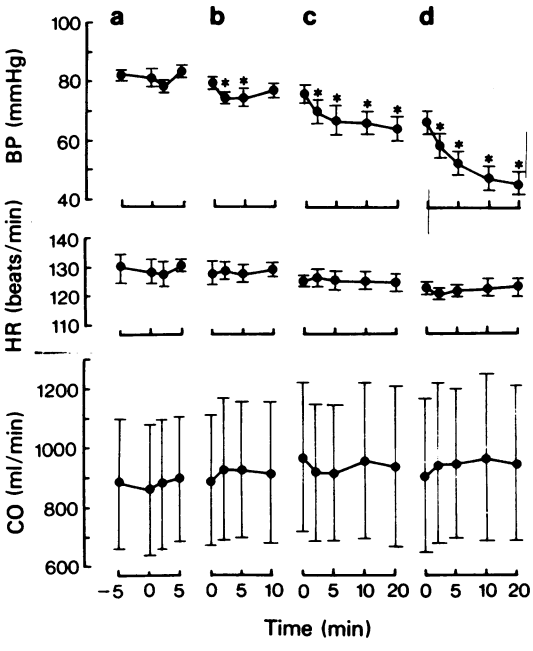

Figure 2 Effect of labetalol on blood pressure (BP), heart rate (HR), and cardiac output (CO) in 4 anaesthetized dogs following vagotomy, adrenalectomy and spinal cord section. A constant i.v. infusion of angiotensinamide (0.025 μg kg^{-1} min^{-1}) was used to enhance vascular tone and support blood pressure. Sequential doses of 0.01, 0.1 and 1 mg/kg i.v. of labetalol were administered in panels (a), (b) and (c) respectively and hydralazine (1 mg/kg, i.v.) was administered in panel (d). Drugs were injected at time zero. Asterisk indicates a significant effect ($P < 0.05$).

propranolol (1 mg/kg i.v.) and phentolamine (10 to 15 mg/kg i.v.), were 131 ± 5 mmHg, 163 ± 6 beats/min and 110 ± 5 mmHg, respectively, whereas after administration of both antagonists, they were 78 ± 7 mmHg, 114 ± 7 beats/min, and 154 ± 6 mmHg, respectively. The difference was statistically significant ($P < 0.05$) in each case. Changes in perfusion pressure elicited by isoprenaline (1 μg i.a.) and noradrenaline (1 μg i.a.) were inhibited 82 ± 4% and 92 ± 2%, respectively, by these antagonists.

Doses of 0.3, 1, 3 and 10 mg intra-arterially of labetalol produced a dose-related decrease in perfusion pressure in the isolated perfused gracilis muscle indicating vasodilatation since flow was kept constant (Table 1). These doses were without effect on systemic blood pressure and heart rate. Similarly, 0.3, 1, and 3 mg of diazoxide also decreased perfusion pressure in this preparation without eliciting a systemic effect. The major portion of each response, produced by these two drugs, disappeared rather quickly following a given dose as indicated by the short time (5.3 min) required for the response to return to 50% of the pre-drug level (Table 2). However, complete recovery, i.e., time required for the response to return to 90% of the pre-drug level, took much longer at any given dose as indicated also in Table 2. In order to compare the vasodilator potencies of the two drugs, the results were expressed as a percentage of the maximum vasodilatation (−67 ± 4 mmHg) produced by nitroglycerine (0.03 or 0.1 mg, i.a.). The doses (i.a.) of labetalol and diazoxide required to produce half-maximal vasodilatation were 1.5 mg (95% CL = 1.2, 1.8) and 0.7 mg (95% CL = 0.5 and 1.0), respectively. Hence, labetalol was found to be less potent than diazoxide by a factor of 0.47 but its effects were longer lasting (Table 2).

Table 1 Maximum changes in perfusion pressure elicited by labetalol and diazoxide in the perfused gracilis muscle[a] of the dog

	Change in perfusion pressure (mmHg, $\bar{x}$ ± s.e.)	
Dose (mg i.a.)	*Labetalol (n = 6)*	*Diazoxide (n = 5)*
0.1	−1.8 ± 0.9	−1.6 ± 0.7
0.3	−6.7 ± 1.6	−11.2 ± 3.4
1.0	−26.5 ± 3.2	−56.0 ± 7.1
3.0	−51.3 ± 4.6	−78.6 ± 9.3
10.0	−70.4 ± 2.9[b]	—

[a] Muscle was isolated *in situ*, acutely decentralized and pretreated with α- and β-adrenoceptor blocking doses of propranolol and phentolamine.
[b] $n = 5$, dose was not given in one experiment.

Discussion

Labetalol is considered to act solely by peripheral α- and β-adrenoceptor antagonism (Farmer *et al.*, 1972; Koch, 1976; Brittain & Levy, 1976; Brogden *et al.*, 1978; Richards & Prichard, 1978). Yet, its antihypertensive effectiveness in man is greater than would be predicted, based solely on this mechanism (Dollery, 1976). Some other action may contribute to the antihypertensive action of labetalol. Dargie, Dollery & Daniel (1976) showed that labetalol can lower blood pressure in rabbits when administered intracisternally, suggesting a CNS component. However, in the present study, labetalol was shown to be no more effective given into the vertebral artery than the femoral vein of dogs, suggesting the lack of a CNS component following systemic administration, since centrally acting hypotensive drugs, such as clonidine, are more effective when given into the vertebral artery compared to the femoral vein (Stattler & Van Zwieten, 1967; Constantine & McShane, 1968). This is in agreement with the report of Martin, Hopkins & Bland (1976) that labetalol, given systemically, does not readily penetrate the blood brain barrier of rats and dogs.

Our studies show that single injections of labetalol decreased perfusion pressure in the perfused gracilis muscle of the dog indicating vasodilatation. The mechanism of vasodilatation seems to be direct and independent of any action involving adrenergic nerves or adrenoceptors since it occurred in spite of decentralization and practically complete α- and β-adrenoceptor blockade. The duration of maximum vasodilatation was proportionately short but the time required for complete recovery suggests an action on vascular smooth muscle of sufficient duration to be important, considering that each dose was injected over a few seconds and then continuously washed out of the muscle. It should be kept in mind that regional blood concentrations obtained with intra-arterial injections (via the perfusion circuit) of labetalol into the gracilis muscle are unlikely to be obtained when the drug is given systemically, unless it selectively accumulates in the vascular smooth muscle. Currently, this information is not available. It remains possible, that the different regional blood concentrations may not be as great as first expected since, in our experience, a similarity exists between active dose intra-arterially (via perfusion circuit) and active dose intravenously per dog weight. The hypertensive action of labetalol without a concomitant decrease in cardiac output in dogs devoid of adrenergic tone also suggests direct vasodilatation as a component of the hypotensive action of labetalol *in vivo*. This is in agreement with the preliminary report of Johnson, Priola & Ehrreich (1977) revealing a hypotensive effect of labetalol in dogs following pretreatment with both α- and β-adrenoceptor antagonists and the recent report of Sweet, Solar & Gaul (1979) showing a sustained vasodilatation by labetalol (0.1 to 0.8 mg, i.a.) in the perfused dog hind limb that appeared independent of its adrenoceptor antagonist activity.

The increase in heart rate observed with the low dose (0.03 mg/kg i.v.) of labetalol in dogs anaesthetized with chloralose was unexpected since labetalol was shown to be without intrinsic sympathomimetic activity in syrosingopine pretreated dogs (Farmer *et al.*, 1972; Brittain & Levy, 1976). Occurrence of the increase in heart rate without a concomitant decrease in blood pressure suggests it is not reflexly mediated. Drew (1978) reported that labetalol (0.3 to 1 μg/ml) depressed the twitch response to electrical stimulation of the cholinergic innervation of guinea-pig isolated ileum both in the presence and the absence of propranolol and without altering the inhibitory action of clonidine on the residual twitch response. He attributed this action to the direct myodepressant properties of labetalol; however, at the concentrations he

Table 2 Duration of vasodilatation elicited by labetalol and diazoxide in the perfused gracilis muscle of the dog

	50% recovery time (min)		*90% recovery time (min)*	
Dose (*mg, i.a.*)	*Labetalol* ($n = 6$)	*Diazoxide* ($n = 5$)	*Labetalol* ($n = 6$)	*Diazoxide* ($n = 5$)
0.1	0.7 ± 0.1[a,b]	0.2 ± 0.03	3.7 ± 1.9	0.7 ± 0.2
0.3	1.7 ± 0.2[b]	0.4 ± 0.04	6.6 ± 2.4[b]	0.8 ± 0.2
1.0	1.9 ± 0.2[b]	0.5 ± 0.1	16.2 ± 4.3[b]	2.0 ± 0.7
3.0	2.2 ± 0.2[b]	5.3 ± 1.3	24.7 ± 5.0	16.5 ± 2.8
10.0	4.5 ± 1.4	—	26.2 ± 5.1[c]	—

[a] Shown are $\bar{x} \pm$ s.e.
[b] Significant difference from diazoxide by *t*-test.
[c] $n = 5$, dose was not give in one experiment.

used, this is unlikely since much higher concentrations are required for negative inotropic activity (Farmer *et al.*, 1972). An alternate explanation could be an action of labetalol inhibiting transmitter (acetylcholine) release. There is substantial evidence in isolated tissues that labetalol can release noradrenaline from adrenergic nerve endings (Doggerell & Paton, 1978a and b; Drew, Levy & Sullivan, 1979) which could either act directly on the sinus node to increase heart rate or on prejunctional α_2-adrenoceptors on the vagus to impede vagal tone and indirectly increase heart rate (Drew 1977; 1978). The absence of a labetalol-induced tachycardia in pentobarbitone anaesthetized dogs (Farmer *et al.*, 1972; Brittain & Levy, 1976) may be attributed to the known inhibition of parasympathetic ganglionic transmission by pentobarbitone (Page & McCubbin, 1965; Olmstead & Page, 1966) precluding manifestations of additional vagal inhibition. In addition, there is indirect evidence that sub-blocking doses of β-adrenoceptor blocking drugs release adrenal catecholamines (Regoli, 1970) in rats which could also explain the tachycardia.

These results suggest that the hypotension produced by systemically administered labetalol does not involve an action in the brain. Also, labetalol in sufficient amounts directly dilates resistance vessels, and this action is independent of its adrenoceptor blocking properties. Such a direct vasodilator action may be an important component of the hypotensive action of labetalol.

We are grateful to Allen Hanburys Ltd. for their generous supply of labetalol. We also wish to recognize the expert technical assistance of Mr Michael Manheim and Mr Ronald Lucas in the performance of these experiments.

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(Received August 22, 1979.
Revised November 20, 1979.)