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Cardiac and renovascular effects in the anaesthetized dog of BW A575C: a novel angiotensin converting enzyme inhibitor with β-adrenoceptor blocking properties

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1 In the anaesthetized open-chest dog, BW A575C (N-(1-(S)-carboxy-5-[4(3- isopropylamino-2-(**R,S**)-hydroxypropoxy)indole-2-carboxamido]pentyl)-(**R,S**)-alanyl-(**S**)-proline) causes a dose-dependent inhibition of the isoprenaline response (increased cardiac rate). In this preparation BW A575C is approximately 50 times less active than propranolol, and 500 times less active than pindolol at the cardiac β_1-adrenoceptor.

2 At equieffective cardiac β_1-adrenoceptor blocking doses in the anaesthetized, open-chest dog, BW A575C (5.0 mg kg^{-1}, i.v.) significantly reduces diastolic blood pressure and reduces cardiac contractility and rate. By contrast, propranolol (0.1 mg kg^{-1}, i.v.) and pindolol (0.01 mg kg^{-1}, i.v.) have little effect on diastolic blood pressure, but significantly reduce cardiac contractility and rate. The effects of BW A575C on cardiac rate are not significantly different from those of propranolol and pindolol, but its effects on cardiac contractility are significantly less than those of propranolol. BW A575C also produces some increase in left ventricular internal dimensions at end-diastole. This small cardiac dilatation is not significantly different from that observed with pindolol but is significantly less than that of propranolol.

3 In the anaesthetized closed-chest dog, BW A575C causes a dose-dependent inhibition of the angiotensin I pressor response. In this preparation BW A575C is approximately equiactive with enalapril at preventing the pressor response due to conversion of exogenous angiotensin I to angiotensin II (inhibition of angiotensin converting enzyme (ACE)).

4 At equieffective ACE-inhibition doses in the anaesthetized, closed-chest dog, BW A575C (1.0 mg kg^{-1} by i.v. infusion) significantly reduces diastolic blood pressure, cardiac contractility and rate, whereas enalapril (1.0 mg kg^{-1} by i.v. infusion) only significantly reduces diastolic blood pressure. This blood pressure lowering effect of enalapril is not significantly different from that of BW A575C. In this preparation BW A575C and enalapril also significantly increase renal blood flow, and renal excretion of urine and Na^+. There is however no significant difference between their renovascular effects.

5 These studies demonstrate that BW A575C produces changes in cardiac and renovascular function which can be ascribed to its being an ACE-inhibitor and a β-adrenceptor blocking agent. The combination of these pharmacological properties results in a fall in blood pressure without compromising either cardiac performance or renal function.

Introduction

The cardiovascular responses to angiotension converting enzyme (ACE) inhibition (Johnston, 1984) or β-adrenoceptor blockade (Prichard & Owens, 1984) are now well-documented. The acute administration of an ACE-inhibitor to both normotensive and hypertensive animals results in a fall in blood pressure and peripheral resistance, which may be associated with some increase in heart rate. The hypotensive effects of ACE-inhibitors are enhanced by prior Na^+-depletion or diuretic treatment (Bengis *et al.*, 1978; Morton *et al.*, 1980; Laubie *et al.*, 1984; Schriffin *et al.*, 1981; 1984; Sweet & Ulm, 1984; Olsen & Meydrech, 1985). ACE-

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inhibitors have also been shown to affect renal function, increasing renal blood flow and the excretion of salt and water (McCaa *et al.*, 1978; Meggs & Hollenberg, 1980; McCaa & Gillespie, 1984; Sweet & Ulm, 1984; Olsen & Meydrech, 1985).

By contrast, the acute administration of a β-adrenoceptor blocking agent to normotensive and hypertensive animals does not always result in a fall in blood pressure, and may even increase peripheral resistance. The most consistent effects of a β-adrenoceptor blocking agent are to reduce cardiac output and heart rate (Nies *et al.*, 1973; Garvey & Ram, 1975; Burden & Hamilton, 1976; Buckingham & Hamilton, 1980; Cohn, 1983). Although β-adrenoceptor blockade is not generally noted for any effects on renal function, it has been reported that β-adrenoceptor blocking agents can impair renal function, possibly through a reduction in renal blood flow, and an increase in Na^+-reabsorption (Nies *et al.*, 1971; 1973; Abdel-Razzak, 1977; Nomura *et al.*, 1978).

Clearly, the cardiac and renovascular responses to an ACE-inhibitor differ from those to a β-adrenoceptor blocking agent. It was therefore of considerable interest to examine the haemodynamic effects of BW A575C (N-(1-(S)-carboxy-5-[4(3-isopropylamino-2-(-R,S)-hydroxypropoxy)indole-2-carboxamido] pentyl)-(R,S)-alanyl-(S)-proline), a novel ACE-inhibitor with β-adrenoceptor blocking properties (Allan *et al.*, 1986a; 1987a). In the studies described in this paper, we have compared the cardiac and renovascular responses to BW A575C, with those of the ACE-inhibitor, enalapril, and the β-adrenoceptor blocking agents, propranolol and pindolol. Some of these results have been previously communicated to the British Pharmacological Society, at its summer meeting in Amsterdam, 1986 (Allan *et al.*, 1986b).

Methods

Cardiac and β-adrenoceptor blockade studies in the anaesthetized, open-chest dog

Normotensive beagle dogs (Cambell Farm, Interfauna Group) of either sex (12–15 kg) were anaesthetized initially with an intravenous injection of sodium thiopentone (30 mg kg^{-1}; M & B) via a cephalic vein. Polythene cannulae were then placed in both femoral veins (for the administration of drugs and anaesthetic), and subsequent anaesthesia maintained by intravenous injection of sodium pentobarbitone (6 mg kg^{-1}; Sagatal, M & B) and α-chloralose (15 mg kg^{-1}; Koch-Light). Each animal was pump ventilated via a tracheotomy tube (tidal volume = 200–250 ml; ventilation rate = 20 min^{-1}).

A polythene cannula, containing heparinised saline, was placed in the abdominal aorta via the right femoral artery, and attached to a blood pressure transducer (Statham) for the measurement of systemic blood pressure. From a left lateral approach, the thorax was opened between ribs 5 and 6, and a partial pericardial cradle fashioned on the dorsal side of the thoracic cavity only, to allow access to the left ventricle of the heart. Two pairs of miniature, ultrasonic crystals (Epicardial patch, 2.5 mm crystal diameter; Triton Technology Inc., San Diego, California) were sutured onto the epicardial surface of the left ventricle so as to permit continuous measurement of the external dimensions for the long and short axes of the left ventricle throughout each cardiac cycle. A further pair (one epicardial patch, one segment length, 2.5 mm crystal diameter), were also attached to the left ventricle, and positioned in approximately the same cardiac plane as the epicardial pair of crystals used to measure the short axis, so as to permit continuous measurement of wall thickness throughout each cardiac cycle. Each pair of ultrasonic crystals were connected to a four channel sonomicrometer (Model 120, Triton Technology Inc., San Diego, California) and calibrated to allow instantaneous measurement of the cardiac dimensions. Finally, a specially designed, short, stiff, left ventricular cannula was introduced into the left ventricular chamber via the apex of the heart, secured by purse-string suture, and connected to a blood pressure transducer to measure left ventricular pressure. A piece of polythene film was placed over the thoracic opening to prevent excessive heat and moisture loss and a 60 min equilibration period begun.

Each animal was maintained at 37°C (body/rectal temperature) by a heated underblanket. Arterial blood samples were taken and the blood gases analysed (Radiometer Blood Gas Analyser) to ensure that blood gases were maintained within acceptable limits (Green, 1979). All measured cardiovascular parameters (systemic blood pressure, left ventricular pressure and its first derivative, LV$dP/dt$, and heart rate), and cardiac dimensions (left ventricular external dimensions [long and short axes] and wall thickness) were recorded continuously on a polygraph (Gould 2800s). Left ventricular internal dimensions were calculated from the measured external dimensions and wall thickness using the simple formula:-

mean left ventricular end-diastolic internal dimension = mean left ventricular end-diastolic external dimension − (2 × mean left ventricular end-diastolic wall thickness).

For mean end-systolic internal dimensions, the same formula was applied but end-systolic external dimensions and wall-thickness were used.

As wall-thickness was always measured in approximately the same cardiac plane as the left ventricular short axis, then the calculated left ventricular internal dimensions are most accurate at the short axis. As

resting wall thickness in non-contracting, excised dog hearts was found to be more uniform, in the left ventricle, than was expected we have also used the short axis measurements of wall-thickness to calculate left ventricular internal dimensions at the long axis. These have been found to exhibit similar changes to those observed at the short axis. However, the observed changes in left ventricular internal dimensions [short axis] have been emphasised in describing the results of the studies reported in this paper.

The effects of BW A575C (0.1–5.0 mg kg^{-1}, i.v.), propranolol (0.01–1.0 mg kg^{-1}, i.v.) and pindolol (0.01–1.0 mg kg^{-1}, i.v.) on cardiac function were assessed by measuring the changes in recorded parameters following the intravenous administration of each dose (in ascending order) and comparing these with control values of these parameters. In each preparation, a dose-response curve to one of these compounds only, was obtained, and the effects of each dose were allowed to stabilize for at least 30 min before the next dose was adminstered.

The cardiac β_1-adrenoceptor blocking activity of these compounds was assessed in the same preparations used to assess their cardiac effects. A logarithmic dose-response (increased heart rate) curve was obtained by administering bolus injections of isoprenaline (0.01–0.3 μg kg^{-1}, i.v.) before and after, each bolus dose of BW A575C, propranolol or pindolol.

Renovascular and ACE-inhibition studies in the anaesthetized, closed-chest dog

Normotensive beagle dogs of either sex (12–15 kg) were anaesthetized, tracheotomized and pump-ventilated as described above. Polythene cannulae were placed in both femoral veins (for the administration of drugs and anaesthetic), in the right external jugular vein (for infusions) and in the abdominal aorta, via the right femoral artery. The tip of the latter cannula was positioned such that it lay above the junction of the renal arteries with the aorta, and was connected to a blood pressure transducer (Statham) for the measurement of systemic blood pressure at the level of the kidneys (i.e. renal perfusion pressure). A pressure-tip transducer (Millar 5F) was then passed down the left carotid artery and into the left ventricular chamber for the measurement of left ventricular pressure and its first derivative, LV$dP/dt$.

For those preparations where renovascular and renal function studies were carried out, a continuous infusion of saline (0.9% at 0.1 ml kg^{-1} min^{-1}) was maintained throughout the surgical preparation and experimental periods, in order to promote a mild diuresis, and the following additional surgery carried out. Each animal was supported at the dorsal processes from selected lumbar vertebrae so as to maintain the animal in an upright (normal) position. From bilateral flank incisions, both kidneys were exposed and cleared of connective tissue and fat. Both renal arteries were located and cleared, to allow access to the sections proximal to the abdominal aorta but without damaging the renal nerve bundles. Electromagnetic flow probes (2.0–3.0 mm: Statham) were then attached to these arteries, for the measurement of renal blood flow. Both ureters were also cleared and cannulated to allow continous collection of urine.

On completion of the surgery, a piece of polythene film was placed over each flank incision to prevent excessive heat and moisture loss and the animals allowed to equilibrate. Each preparation was maintained at 37°C (body/rectal temperature), by a heated underblanket or infra-red lamp, and blood gases were analysed to ensure they were maintained at acceptable levels (Green, 1979). All measured cardiovascular parameters (systemic blood pressure, left ventricular pressure and its first derivative LV$dP/dt$, heart rate, and renal blood flow) were recorded continuously on a polygraph (Grass Model 7D). Timed collections of urine into preweighed glass vials were made before and during administration of inhibitor drugs. These urine samples were later analysed both for volume (by weight), and Na^+ content (Corning 460 Automatic Flame Photometer) and then the rate of excretion of urine Na^+ calculated.

The effects of an i.v. infusion of either BW A575C or enalapril (both at 0.02 mg kg^{-1} min^{-1}) on the renovascular system in this preparation were assessed by measuring the changes in the recorded cardiovascular parameters and renal function. For these studies i.v. infusion of these compounds was considered to be the most appropriate method of administration so that renal function measurements could be made in the absence of any abrupt cardiovascular changes.

As a concurrent assessment of the ACE-inhibition properties of BW A575C and enalapril could not be carried out in the studies described above, this assessment was made in additional preparations where no measurement of renal blood flow or renal function were made. These preparations also received no i.v. saline infusion. A logarithmic dose-response (pressor) curve was obtained by administering bolus injections of angiotension I (0.1–1.0 μg kg^{-1}, i.v.) before and after each bolus dose (in ascending order, 0.01, 0.1 and 1.0 mg kg^{-1}, i.v.) of either BW A575C or enalapril.

Analysis of data

Data are presented as means and standard errors, and were analysed using local software compiled by the Computing and Statistical Services Department at the Wellcome Research Laboratories, Beckenham. The statistical significance of the cardiac or renovascular effects of BW A575C, propranolol, pindolol or enalapril were assessed by application of the analysis

of variance test (two-way).

For the comparison of these effects of BW A575C with those produced by equieffective doses of propranolol, pindolol or enalapril, the analysis of variance test (one-way) was used. Further assessment of the statistical significance was by use of the unpaired Student's t test. Statistical significance was assumed at P values <0.05.

In those experiments where logarithmic dose-response curves were obtained, these were derived from the mean responses from a group of animals. Where it was possible to derive dose-ratios from these logarithmic dose-response curves, a regression analysis (using local software) has been applied. Dose-ratios are presented as means with 95% confidence limits.

Drugs used

Angiotensin I, isoprenaline, pindolol and propranolol were all obtained from Sigma Chemicals Ltd. Enalapril was the generous gift of Merck, Sharp and Dohme Ltd.

All drugs were dissolved either in distilled water, or saline (0.9%) and where administered as bolus i.v. injections, in volumes of 0.1 ml kg^{-1}.

Results

Cardiac effects in the anaesthetized, open-chest dog

The intravenous administration of BW A575C (0.1–5.0 mg kg^{-1}) produced dose-related effects in this preparation ($n = 5$). BW A575C caused reductions in systolic and diastolic blood pressure, heart rate, and LV$dP/dt$, and an increase in both left ventricular end-diastolic and end-systolic internal dimensions (see Figure 1). Analysis of variance showed these effects to be statistically significant for systolic ($F = 21.2$, $P<0.05$) and diastolic ($F = 22.7$, $P<0.05$) blood pressure, heart rate ($F = 5.0$, $P<0.05$) and left ventricular end-diastolic ($F = 10.8$, $P<0.05$) and end-systolic ($F = 4.3$, $P<0.05$) internal dimensions [short axis].

The intravenous administration of propranolol (0.01–1.0 mg kg^{-1}) also produced dose-related effects in this preparation ($n = 5$). Propranolol caused little change in blood pressure except at its highest dose, where it caused a reduction in systolic (163 ± 13 to 137 ± 16 mmHg) and diastolic (100 ± 9 to 89 ± 12 mmHg) blood pressures. However, analysis of variance showed no statistically significant effects of propranolol upon blood pressure. By contrast, however, propranolol caused dose-related reductions in heart-rate (207 ± 7 to 150 ± 8 beats min^{-1} at 1.0 mg kg^{-1}) and LV$dP/dt$ (3263 ± 231 to 1613 ± 221 mmHg s^{-1} at 1.0 mg kg^{-1}), and increases in both left ventricular end-diastolic (32.7 ± 4.5 to 38.1 ± 4.5 mm at 1.0 mg kg^{-1}) internal dimensions [short axis]. Analysis of variance showed these effects to be statistically significant for heart rate ($F = 30.7$, $P<0.05$), LV$dP/dt$ ($F = 52.6$, $P<0.05$), and left ventricular end-diastolic ($F = 21.6$, $P<0.05$) and end-systolic ($F = 61.3$, $P<0.05$) internal dimensions [short axis].

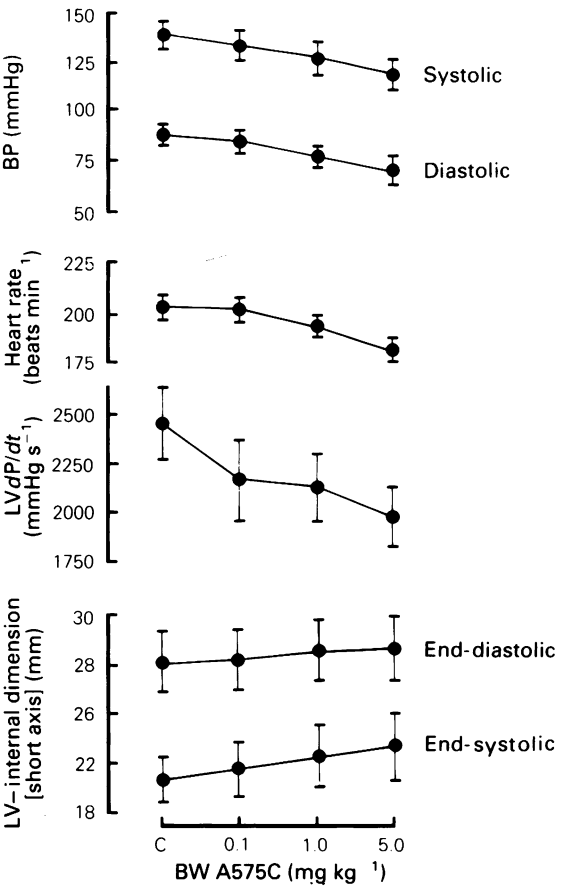

Figure 1 Effects of BW A575C on blood pressure, cardiac function and dimensions, in the anaesthetized, open-chest dog. All values are the mean of 5 animals; s.e.mean shown by vertical lines.

The intravenous administration of pindolol (0.01–1.0 mg kg^{-1}) caused a more complex series of effects in this preparation ($n = 5$). Pindolol caused dose-related reductions in blood pressure. At the highest dose, pindolol markedly reduced both systolic (137 ± 6 to 113 ± 7 mmHg) and diastolic (83 ± 5 to 65 ± 5 mmHg) blood pressures. Only at the lower

doses did pindolol reduce heart rate (203 ± 10 to 177 ± 11 beats min^{-1} at 0.1 mg kg^{-1}) and LV$dP/dt$ (3362 ± 364 to 2488 ± 429 mmHg s^{-1} at 0.1 mg kg^{-1}), and increased both left ventricular end-diastolic (28.2 ± 1.3 to 29.8 ± 1.1 mm at 0.1 mg kg^{-1}) and end-systolic (20.0 ± 1.3 to 21.2 ± 1.5 mm at 0.1 mg kg^{-1}) internal dimensions [short axis]. Although increasing the dose of pindolol produced some reversal of these effects, analysis of variance found these effects to be statistically significant for systolic ($F = 15.9$, $P < 0.05$) and diastolic ($F = 26.9$, $P < 0.05$) blood pressures, heart rate ($F = 3.6$, $P < 0.05$), LV$dP/dt$ ($F = 4.1$, $P < 0.05$) and left ventricular end-diastolic ($F = 5.8$, $P < 0.05$) internal dimensions [short axis].

Cardiac β_1-adrenoceptor blocking effects in the anaesthetized, open-chest dog

BW A575C, propranolol and pindolol all caused dose-related inhibition of the isoprenaline-induced increase in heart rate and LV$dp/dt$. Using the displacement of the logarithmic dose-heart rate response curve to isoprenaline as an indicator of cardiac β_1-adrenoceptor blockade, regression analysis showed that a similar dose-ratio was achieved for 5.0 mg kg^{-1} BW A575C, 0.1 mg kg^{-1} propranolol and 0.01 mg kg^{-1} pindolol. The dose-ratios (with 95% confidence limits) were 3.3 (2.2–5.5), 3.8 (2.1–8.7) and 3.6 (2.2–7.1), respectively (see Figure 2).

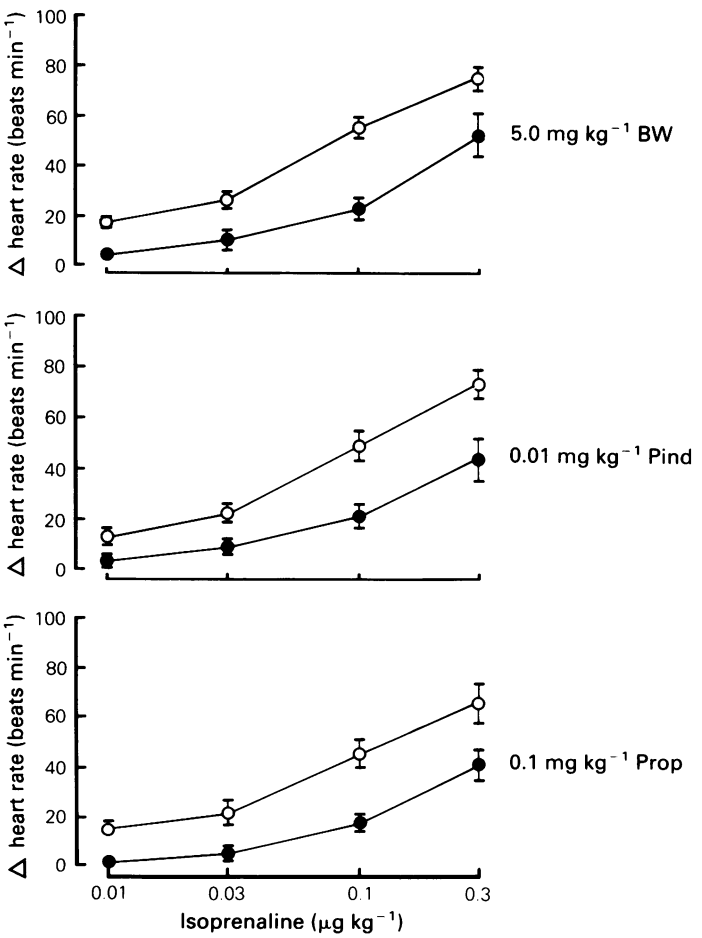

Figure 2 Effects of BW A575C (BW), pindolol (Pind) and propranolol (Prop) on the isoprenaline-induced heart rate increase in the anaesthetized open-chest dog. All values are the mean of 6 animals; s.e.mean shown by vertical lines.

Comparison of the cardiac effects at equieffective cardiac β_1-adrenoceptor blocking doses in the anaesthetized, open-chest dog

Approximately equieffective cardiac β_1-adrenoceptor blockade was achieved by 5.0 mg kg^{-1} BW A575C, 0.1 mg kg^{-1} propranolol, and 0.01 mg kg^{-1} pindolol. At these doses, analysis of variance showed a significantly greater reduction in diastolic blood pressure with BW A575C compared with propranolol ($F = 7.3$, $P < 0.05$) and pindolol ($F = 83.1$, $P < 0.05$), but no difference in heart rate reduction. Similarly, there was no difference between the reductions in LV*dP/dt* with BW A575C and pindolol, however there was a significantly greater reduction with propranolol ($F = 6.5$, $P < 0.05$). Although BW A575C caused a small increase in left ventricular end-diastolic and end-systolic internal dimensions [short axis] these were not significantly different from those obtained with pindolol, except at end-systole, but were significantly less than those with propranolol, ($F = 5.4$, $P < 0.05$; $F = 5.3$, $P < 0.05$ respectively; see Figure 3). Statistical analysis by unpaired Student's *t* test showed the same differences in the cardiac effects of these compounds.

Renovascular effects in the anaesthetized, closed-chest dog

BW A575C infusion (to a total dose of 2.0 mg kg^{-1} over 100 min) in this preparation ($n = 5$) produced reductions in diastolic blood pressure, heart rate and LV*dP/dt* (Figure 4). In addition, BW A575C caused an increase in renal blood flow, and a reduction in renal vascular resistance (14.9 ± 1.8 to 10.3 ± 1.2 dynes cm^{-5} s), which was accompanied by an increase in urine excretion and Na^+ excretion (Figure 4). These effects were evident within 20 min of starting the infusion, and analysis of variance showed statistical significance in the changes in diastolic blood pressure ($F = 9.7$, $P < 0.05$), heart rate ($F = 13.9$, $P < 0.05$), LV*dP/dt* ($F = 9.3$, $P < 0.05$), renal blood flow ($F = 8.0$, $P < 0.05$) urine excretion ($F = 10.8$, $P < 0.05$) and Na^+ excretion ($F = 9.2$, $P < 0.05$).

Infusion of enalapril (to a total dose of 2.0 mg kg^{-1} over 100 min) in this preparation ($n = 5$), also produced a reduction in diastolic blood pressure (138 ± 13 to 120 ± 12 mmHg at 2.0 mg kg^{-1}) but no change in either heart rate or LV*dP/dt*. This reduction in blood pressure was accompanied by an increase in renal blood flow (293 ± 18 to 417 ± 44 ml min^{-1} at 2.0 mg kg^{-1}) and a reduction in renal vascular resistance (18.3 ± 0.9 to 11.2 ± 0.8 dynes cm^{-5} s at 2.0 mg kg^{-1}). In addition, enalapril also caused an increase in urine excretion (207 ± 5 to 367 ± 59 µl min^{-1} at 2.0 mg kg^{-1}) and Na^+ excretion (25.6 ± 9.5 to 83.4 ± 18.7 mEq min^{-1} at 2 mg kg^{-1}).

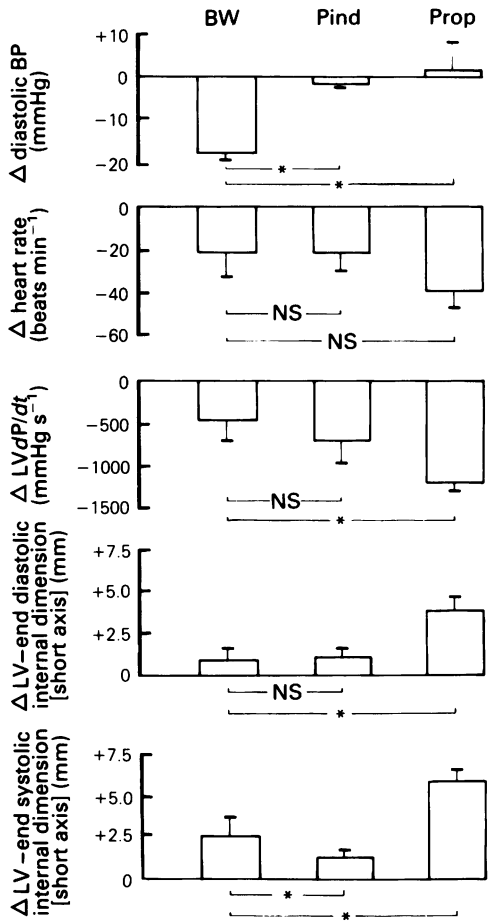

Figure 3 Comparative effects of equieffective β_1-adrenoceptor blocking doses of BW A575C (BW), pindolol (Pind) and propranolol (Prop) on blood pressure, cardiac function and cardiac dimensions in the anaesthetized open-chest dog. All values are the mean of 6 animals; s.e.mean shown by vertical lines. (*Significantly different from response to BW, $P < 0.05$; NS not significantly different by analysis of variance and unpaired Student's *t* test).

Like BW A575C, the effects of enalapril were evident within 20 min of starting the infusion, and analysis of variance showed statistical significance in the changes in diastolic blood pressure ($F = 9.3$, $P < 0.05$), renal blood flow ($F = 19.7$, $P < 0.05$), urine excretion ($F = 3.4$, $P < 0.05$) and Na^+ excretion ($F = 3.3$, $P < 0.05$).

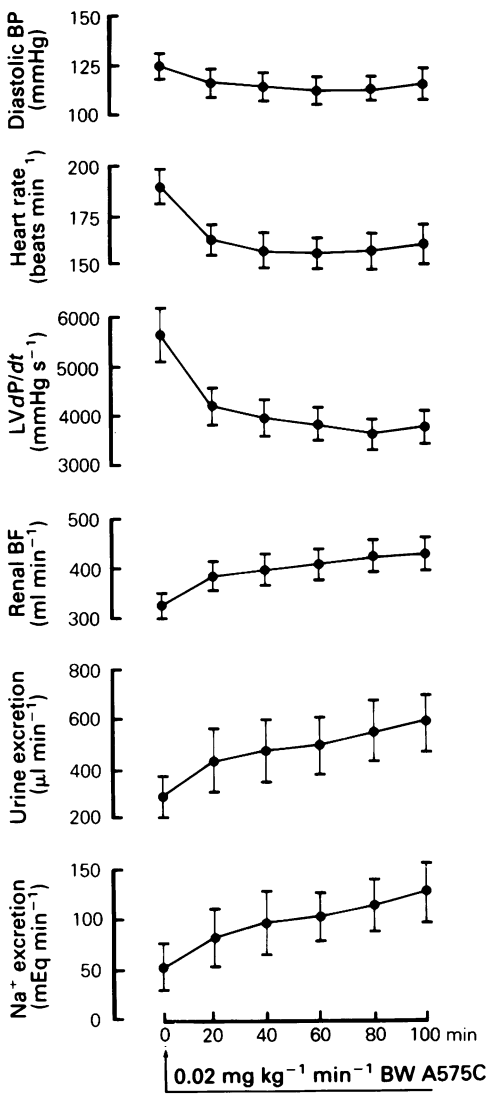

Figure 4 Effects of BW A575C on blood pressure, cardiac and renovascular parameters in the anaesthetized, closed-chest dog. All values are the mean of 5 animals; s.e.mean shown by vertical lines.

ACE-inhibition in the anaesthetized, closed-chest dog

BW A575C and enalapril ($n = 3$ for both compounds) caused a dose-related inhibition of the angiotensin I-induced pressor response. In these studies both BW A575C, and enalapril produced a depression of the angiotensin I logarithmic dose-pressor response curve, thus it was not possible to derive dose-ratios (see Figure 5). However, it was evident from these data that the effects of BW A575C at 1.0 mg kg^{-1} were similar to those of enalapril at 1.0 mg kg^{-1}.

Comparison of the cardiac and renovascular effects at equieffective ACE-inhibition doses in the anaesthetized, closed-chest dog

Approximately equieffective ACE-inhibition was achieved by 1.0 mg kg^{-1} BW A575C and enalapril. At these doses, analysis of variance showed no significant difference in their effects upon diastolic blood pres-

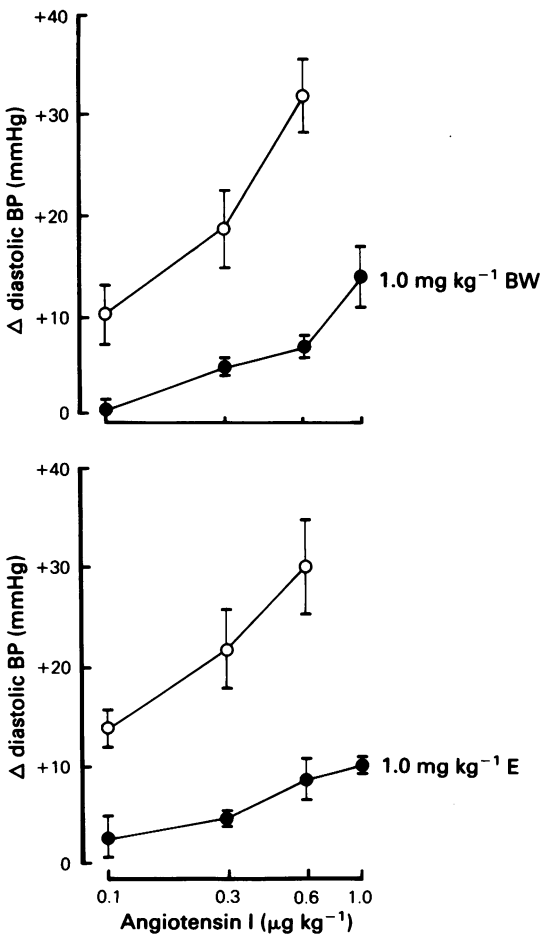

Figure 5 Effects of BW A575C (BW) and enalapril (E) on the angiotensin I-induced pressor response in the anaethetized, closed-chest dog. All values are the mean of 3 animals with s.e.mean shown by vertical lines.

sure, renal blood flow, urine excretion or Na^+ excretion. However, BW A575C produced a significantly greater reduction in heart rate ($F = 28.9$, $P < 0.05$) and LV$dP/dt$ ($F = 5.5$, $P < 0.05$) than enalapril (see Figure 6). Statistical analysis by unpaired Student's t test showed the same differences in the cardiac renovascular effects of these compounds.

Discussion

In the anaesthetized dog, intravenous administration of BW A575C has been shown to produce both ACE-inhibition and cardiac β_1-adrenoceptor blockade at doses which also cause changes in resting cardiac and renovascular parameters. The observation of the dual activity of BW A575C *in vivo* in the studies described in this paper therefore confirms and extends our earlier published studies (Allan *et al.*, 1987a). In open-chest preparations, BW A575C lowers blood pressure, and reduces both cardiac contractility and rate. The cardiac effects are associated with an increase in left ventricular internal dimensions at end-systole and this is consistent with its β-adrenoceptor blockade properties. However, BW A575C causes only small changes in these dimensions at end-diastole. In closed-chest preparations, BW A575C also lowers blood pressure, and reduces both cardiac contractility and rate. In addition, BW A575C causes a reduction in renal vascular resistance and an increase in both renal blood flow and function.

The acute blood pressure lowering and renovascular effects of ACE-inhibitors are well-documented for normotensive and hypertensive animals (Bengis *et al.*, 1978; Antonaccio *et al.*, 1979; Schriffin *et al.*, 1981; 1984; McCaa & Gillespie, 1984; Sweet & Ulm, 1984; Olsen & Meydrech, 1985) and man (Brunner *et al.*, 1979; Gavras *et al.*, 1979; Biollaz *et al.*, 1981; Davies *et al.*, 1984; Abrams *et al*, 1984). Although ACE-inhibitors are not generally noted for any direct effects upon the heart they do appear to produce a lesser reflex tachycardia than would be anticipated from their hypotensive effects. However, this apparent cardiac depression has been explained by the removal of the facilitatory action of endogenous angiotensin II upon the nervous pathways which mediate this reflex (Hatton *et al.*, 1981; Fitzpatrick & Julius, 1985) thus the primary cardiovascular response to ACE-inhibition is sustained by the peripheral vascular beds and may be particularly marked in the kidney (Meggs & Hollenberg, 1980; Davies *et al.*, 1984; Fitzpatrick & Julius, 1985).

The cardiac and renovascular effects of ACE-inhibitors have been verified in our studies with enalapril. In closed-chest preparations, enalapril lowers blood pressure, and increases renal blood flow and function, with little effect upon cardiac contractility or rate. BW A575C shares this profile of effects, but in addition reduces both cardiac contractility and rate. These additional effects can be attributed directly to its cardiac β_1-adrenoceptor blocking properties.

β-Adrenoceptor blocking agents are well-known for

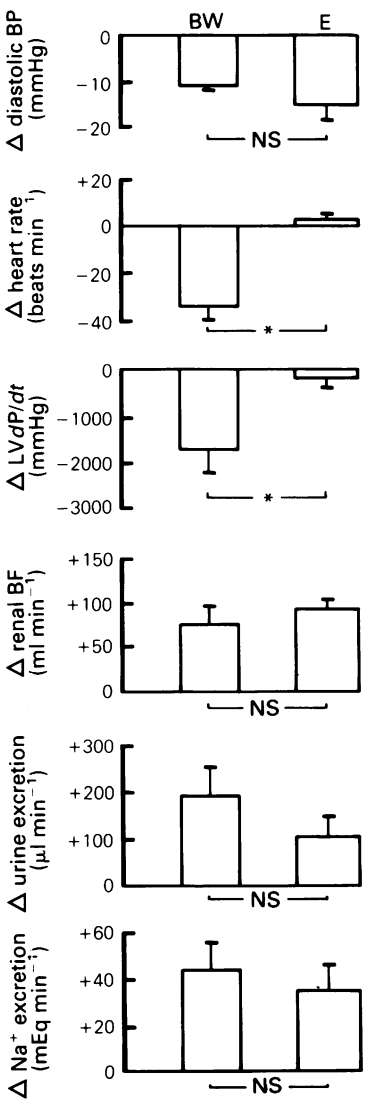

Figure 6 Comparative effects of equieffective angiotensin converting enzyme (ACE) inhibition doses of BW A575C (BW) and enalapril (E) in the anaesthetized closed-chest dog. All values are the mean with s.e.mean shown by vertical lines. (*Significantly different from response to BW, $P < 0.05$; NS not significantly different by analysis of variance and unpaired Student's t test.

their ability to reduce acutely cardiac function in normotensive and hypertensive animals (Nies *et al.*, 1973; Garvey & Ram, 1975; Burden & Hamilton, 1976; Buckingham & Hamilton, 1980; Cohn, 1983) and man (Ulrych *et al.*, 1968; Prichard & Gillam, 1969; Hansson, 1973). This reduction in cardiac function has also been shown to be associated with an increase in cardiac dimensions (Chamberlain, 1966; Helfant *et al.*, 1971). β-Adrenoceptor blocking agents with partial agonist activity (notably at vascular β_2-adrenoceptors) have been shown to lower blood pressure after acute administration. However, this cannot be said for β-adrenoceptor blocking agents which have little or no partial agonist activity. The cardiac β-adrenoceptor blocking agents invariably require chronic administration before their blood pressure lowering effects are seen (Scriabine, 1979; Man in't Veld & Schalekamp, 1983; Prichard & Owens, 1984). This has been explained by the initiation of a reflex peripheral vasoconstriction (mediated by the sympathetic nervous system) in response to a reduced cardiac output following acute administration of these agents (Scriabine, 1979; Conway, 1980). In addition to their cardiac effects, some β-adrenoceptor blocking agents have been reported to reduce both renal blood flow and function, after acute administration, in both animals (Nies *et al.*, 1971; Abdel-Razzak, 1977; Nomura *et al.*, 1978) and man (Zech *et al.*, 1975; Sullivan *et al.*, 1976; Wilkinson, 1982). This renovascular effect may be a contributory factor in the increased vascular resistance seen with these agents.

The cardiac effects of two different β-adrenoceptor blocking agents, propranolol (β_1/β_2–with little partial agonist activity) and pindolol (β_1/β_2–with marked partial agonist activity) have been verified in our studies. In open-chest preparations, propranolol produces little change in blood pressure, reduces cardiac contractility and rate, and increases left ventricular internal dimensions (particularly at end-diastole). By contrast, pindolol lowers blood pressure, but only reduces cardiac contractility and rate at low doses. With increasing doses of pindolol, the reduction in cardiac function is reversed. A similar pattern is seen in the effects of pindolol upon left ventricular end-diastolic internal dimensions. BW A575C also reduces cardiac contractility and rate, but produces only small increases in left ventricular end-diastolic internal dimension, and lowers the blood pressure. In this respect BW A575C differs from propranolol, but shows some similarity to pindolol. For both BW A575C and pindolol, their relatively small increases in left ventricular end-diastolic internal dimensions can be explained by their ability to lower blood pressure and consequently to unload the heart. This can be ascribed to the marked partial agonist activity of pindolol. However there is no evidence either *in vitro* or *in vivo*, to support any such activity for BW A575C. This can therefore be ascribed to its ACE-inhibitor properties.

The rationale for developing compounds which possess more than one pharmacological property is based on the finding that many disease states require multiple drug therapy. However, it has not proved to be an easy task to introduce two dissimilar pharmacological properties into a single molecule. The discovery of BW A575C, which possesses both ACE-inhibitory and β-adrenoceptor blocking properties, and the recent, as yet unpublished, observations (Allan *et al.*, 1987b) that this molecule is active as a single entity, makes BW A575C particularly interesting. It therefore represents a novel addition to the list of compounds intended for the treatment of cardiovascular disease. ACE-inhibition and β-adrenoceptor blockade are established antihypertensive therapies but neither therapy is completely effective when used alone to control blood pressure (Zanchetti *et al.*, 1983). Both ACE-inhibitory and β-adrenoceptor blocking moieties were incorporated in a single molecule with a view to determining whether or not the efficacies of the individual therapies might be retained while reducing or eliminating some of their less desirable features i.e. release of renin (ACE-inhibitors), cardiac dilatation (β-adrenoceptor blocking agents) (see also Allan *et al.*, 1987a). Recent clinical studies have confirmed that a combination of an ACE-inhibitor with a β-adrenoceptor blocking agent is a more effective antihypertensive therapy than either alone (Pickering *et al.*, 1982). For this reason it was important to establish whether or not the combination of pharmacological properties found in BW A575C would be expressed satisfactorily within the cardiovascular system. From the studies described in this paper it is evident that BW A575C does produce changes in cardiac and renovascular parameters which can be ascribed to its being both an ACE-inhibitor and a cardiac β_1-adrenoceptor blocking agent. The combination of these pharmacological properties allow BW A575C to reduce blood pressure without compromising either cardiac performance or renal function. Clearly, further studies of this novel compound are required to establish its clinical potential.

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