J. Pharm. Pharmacol. 1988, 40: 408–414
Received November 6, 1987

Cardiovascular and Renal Actions of Calcium Channel Blocker Chemical Subgroups: a Search for Renal Specificity

RICHARD J. BARRETT, KATHRYN F. WRIGHT, DAVID R. TAYLOR AND ANTHONY G. PROAKIS

Department of Pharmacology, A. H. Robins Research Laboratories, 1211 Sherwood Avenue, Richmond, Virginia 23261, USA

Abstract—The diuretic and natriuretic responses to structurally distinct classes of Ca^{2+} channel blockers have been compared, to determine whether any agent provoked K^+-sparing natriuresis, and to assess the relation of such responses with drug effects on blood pressure. Conscious normotensive Sprague-Dawley rats received vehicle or one of the following drugs in an oral saline load (40 mL kg^{-1}): nifedipine, nimodipine, nitrendipine, prenylamine, cinnarizine, flunarizine, diltiazem, verapamil, hydrochlorothiazide, amiloride, or hydralazine, at doses from 0·316 to 100 mg kg^{-1}. Urine was collected for 6 h. Blood pressure was monitored directly in parallel studies. Diltiazem (31·6, 100 mg kg^{-1}) and flunarizine (100 mg kg^{-1}) enhanced urine and electrolyte excretion in spite of marked hypotension; diltiazem was the only drug to produce dose-related renal responses. In contrast, equihypotensive doses of hydralazine and nifedipine produced overt urine and electrolyte retention. Nitrendipine and prenylamine (0·316 mg kg^{-1} each) produced slight diuresis or natriuresis without altering blood pressure; higher doses had no effect. The 31·6 mg kg^{-1} doses of verapamil, nitrendipine, and nimodipine markedly reduced blood pressure, but neither enhanced nor limited urine and electrolyte excretion. Cinnarizine failed to produce any cardiovascular or renal effects. Diuretic responses evoked by the Ca^{2+} channel blockers were not class-specific, showed no tendency towards sparing K^+, were generally weaker than those produced by low doses of amiloride or hydrochlorothiazide, and were dissociable from drug-induced changes in blood pressure.

Calcium channel blockers may permit monotherapeutic management of hypertension by reducing peripheral vascular resistance without triggering the renal compensation and subsequent tolerance characteristic of classical vasodilator therapy (Gross 1977; Koch-Weser 1979; Brunn et al 1986), and without provoking the metabolic and electrolyte disturbances often associated with diuretic therapy (Ames 1983). A number of chemically distinct Ca^{2+} channel blockers including verapamil (Rosenkranz et al 1984; MacLaughlin et al 1985), diltiazem (Rosenkranz et al 1984; Nagao et al 1985; Narita et al 1983; Johns 1985), and selected dihydropyridines (Rosenkranz et al 1984; Johns 1985; Garthoff et al 1982; Ene et al 1985; Edgar et al 1985) have produced saluretic actions in man and/or animals. Diuresis and natriuresis have not always been accompanied by kaliuresis (DiBona & Sawin 1984; Edgar et al 1985; Ene et al 1985; Zanchetti & Leonetti 1985), a provocative finding which suggests that a Ca^{2+} channel blocker may offer a therapeutic advantage over existing diuretic therapy by provoking diuresis and natriuresis without depleting plasma K^+ levels. Several Ca^{2+} channel blockers have been shown to inhibit the actions of angiotensin II both directly by preventing its vascular and renal haemodynamic responses (Bell & Lindner 1984; Nagao et al 1985), and indirectly by impairing activation of the renin-angiotensin-aldosterone axis (Ichikawa et al 1979; Garthoff et al 1983). Additionally, selected Ca^{2+} channel blockers have been shown to dilate the renal vasculature (Loutzenhiser & Epstein 1985) and also to reduce ischaemia-induced renal pathology (Wait et al 1983; Malis et al 1983; Burke et al 1984). These actions, which would be complementary to any diuretic effects of the drugs, lead to the suggestion that Ca^{2+} channel blockers may prove useful in the treatment of renal impairment and failure.

Most interestingly, distinct therapeutic indications of structurally diverse Ca^{2+} channel blockers have been established by the preferential activity of a compound on cardiac conducting tissues, or on coronary vs systemic blood vessels (Janis & Scriabine 1983; Millard et al 1982). However, the likelihood that a chemical subgroup of Ca^{2+} channel blockers may provoke preferential renal pharmacological actions has not been investigated, although the therapeutic relevance of drug-induced alterations in fluid and electrolyte excretion in hypertensive, anginal, or arrhythmic patients is obvious.

The present investigations were undertaken to quantify and compare the renal excretory responses of representative drugs from structurally and pharmacologically distinct classes of Ca^{2+} channel blockers. The purposes of the study were to determine (i) if one particular agent or structural class exhibited relatively greater diuretic and natriuretic actions than another, (ii) if such actions were dose-responsive, (iii) if kaliuresis was dissociated from natriuresis, and (iv) if the renal actions were influenced by drug-induced alterations in systemic blood pressure.

Materials and Methods

Renal excretory studies

These experiments were performed by a modification of the method of Lipschitz et al (1943) as described by Kau et al (1984), a method that is extremely sensitive to detecting diuretic activity.

Normotensive, adult male Sprague-Dawley rats (Charles River) were homogeneously paired. At least one week

Correspondence to: R. J. Barrett, Dept of Pharmacology, A. H. Robins Research Laboratories, 1211 Sherwood Avenue, Richmond, Virginia 23261, USA.

following pairing, animals were fasted overnight, but allowed free access to water before the experiments. Pairs of rats were randomly assigned to groups (10–12 rats, 2 rats/cage) to receive either a single dose of a test drug or the saline vehicle. Each rat was weighed individually and dosed orally with a 0·9% saline load (40 mL kg^{-1}). Vehicle-treated animals received saline alone, while drug-treated animals received either 0·316, 3·16, 31·6 or 100 mg kg^{-1} of one of the following drugs dissolved or suspended in the saline load: cinnarizine, flunarizine, prenylamine, diltiazem, verapamil, nifedipine, nimodipine, nitrendipine, or hydralazine. For comparative purposes and as positive controls, additional rats were dosed with amiloride or hydrochlorothiazide 3 mg kg^{-1} p.o. Following dosage, pairs of rats were placed in metabolism cages and urine was collected for the next 6 h. Pairs of rats were subjected to a maximum of three treatments; at least one week elapsed between treatments.

The collected urine volume was measured and urine samples were frozen until assayed. Urinary Na^+ and K^+ concentrations were determined with an ion-sensitive electrode (Orion Instruments Model 1020 Na-K Analyzer, Cambridge, MA), and Cl^- concentrations by electrometric titration (Haake-Buchler Digital Chloridometer, Saddle Brook, NJ). Excretion of each electrolyte was calculated as the product of urine concentration and urine volume excreted in mequiv kg^{-1} (sum of two rats)/6 h. Urine volume was calculated as mL kg^{-1}/6 h. Na/K ratio was calculated as the quotient of Na^+ excretion/K^+ excretion ($U_{Na}V/U_KV$). Since urine was collected and pooled from pairs of rats in a cage, n was determined by the number of cages.

In each experiment, two groups of rats received test drugs while a third group was treated with the saline vehicle alone. This design provided control data in each experiment to which drug responses could be compared. Accordingly, results were analysed by analysis of variance and Dunnett's test (Dunnett 1955) for multiple comparisons to a single control. Statistical significance was assigned when $P < 0.05$.

Blood pressure studies

These experiments were performed in parallel to the renal excretory studies under nearly identical conditions. At least 48 h preceding experimentation, normotensive adult, male Sprague-Dawley rats were anaesthetized with sodium pentobarbitone, 50 mg kg^{-1} i.p. A carotid artery was exposed by a ventral cervical incision, and a catheter made of PE-50 (Clay-Adams, Parsippany, NJ) was introduced proximally so that the tip resided in the aortic arch. The catheter was exteriorized at the nape of the neck, filled with heparinized saline (1000 USP units mL^{-1}), and heat sealed.

As in the renal excretory studies, animals were fasted overnight but allowed free access to water before testing. On the morning of the experiment, the arterial catheter was connected to a Statham p23Db pressure transducer via a length of PE-50 tubing, and the pulse pressure was displayed on a Grass polygraph. Animals remained conscious and unrestrained at all times. Animals were allowed to stabilize for approximately 1 h before predose control values were recorded. Drugs were administered orally in a saline load (40 mL kg^{-1}) as in the renal excretory studies. Systolic and diastolic blood pressures were recorded continuously for the next 6 h. Blood pressure studies differed from the renal excretory studies only in that animals were not paired, urine was not collected, and arterial catheters had been implanted before testing. Each animal was subject to only a single treatment. Mean arterial blood pressures [MABP, calculated as (systolic-diastolic)/3 + diastolic] following drug administration were analyzed by analysis of variance and compared with predose control values by Dunnett's test. Statistical significance was assigned when $P < 0.05$.

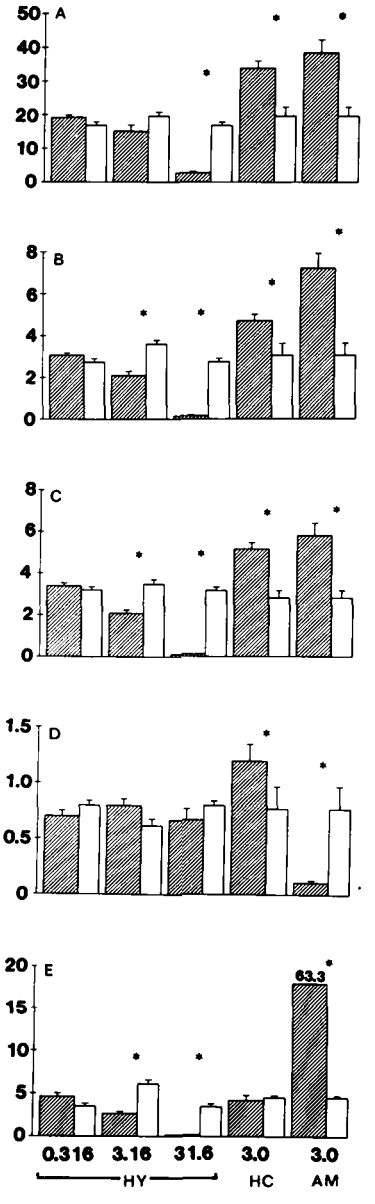

FIG. 1. Urine and electrolyte excretory profile in rats treated with saline (open bars), hydralazine (HY), hydrochlorothiazide (HC), or amiloride (AM) (shaded bars). n = 2 per cage, 5–6 cages per group. Doses as indicated below each bar. * = $P < 0.05$.
Key: A, UV (mL kg^{-1}/6 h)
B, UNaV (m equiv kg^{-1}/6 h)
C, UClV (m equiv kg^{-1}/6 h)
D, UKV (m equiv kg^{-1}/6 h)
E, Na/K.

Drugs used

Drugs and their sources were as follows: nimodipine and

nitrendipine (Bayer); diltiazem (Marion); amiloride (Merck); hydrochlorothiazide, prenylamine, cinnarizine, flunarizine, verapamil, nifedipine, hydralazine (Sigma). All drugs were dissolved or suspended in 0·9% NaCl containing 3–6 drops Tween 80 per 100 mL solution.

Results

The renal excretory responses to saline vehicle were similar in all experiments (open bars in Figs 1–4). Mean arterial blood pressure (MABP) was unchanged over 6 h in vehicle-treated rats (Table 1).

As illustrated in Fig. 1, low doses of hydrochlorothiazide and amiloride produced obvious increments in excretion of urine, Na^+ and Cl^-, but divergent effects on K^+ excretion. The antikaliuretic action of amiloride is reflected in a greatly exaggerated Na/K ratio, while the balanced natriuresis/kaliuresis following hydrochlorothiazide resulted in a Na/K ratio which was similar to that observed in the saline-treated controls.

The lowest dose of the classical vasodilator hydralazine had no effect on renal urine or electrolyte excretion (Fig. 1) or MABP (Table 1), while the higher doses provoked dose-dependent hypotension, antidiuresis and antinatriuresis; K^+ excretion remained unchanged at all doses, resulting in a dose-dependent reduction in the Na/K ratio.

The lowest dose (0·316 mg kg^{-1}) of the dihydropyridines nifedipine and nitrendipine had no discernable effect on MABP (Table 1), and only nitrendipine provoked a slight diuresis (Fig. 2). The 3·16 mg kg^{-1} dose of nifedipine and nitrendipine had no effect on renal excretory patterns nor MABP. Similarly, neither 0·316 nor 3·16 mg kg^{-1} nimodipine influenced MABP and urine and electrolyte excretion. Like hydralazine, the 31·6 mg kg^{-1} doses of nifedipine, nimodipine, and nitrendipine produced marked reductions in MABP (Table 1), but distinctly different renal responses. The high dose of nifedipine caused marked retention of urine, Na^+, and Cl^-, but unlike hydralazine, also produced antikaliuresis, yielding an increased Na/K ratio. In contrast, in spite of relatively similar hypotensive effects, urine and electrolyte secretion were neither inhibited nor enhanced by nitrendipine or nimodipine (Fig. 2).

Cinnarizine failed to alter renal excretory patterns significantly (Fig. 3) and MABP (Table 1) at any of the four doses tested, with the exception of a slight antichlorouretic effect following 3·16 mg kg^{-1}. Although statistically significant, the biological importance of this isolated response is doubtful.

The lower doses of flunarizine (0·316, 3·16, and 31·6 mg kg^{-1}) had no effect on urine and electrolyte excretion (Fig. 3), nor on MABP (Table 1). Clear and significant enhancement of urine and electrolyte excretion was evident following

Table 1. Effects of calcium channel blockers or hydralazine on MABP (mean ± s.e.m.) in conscious saline-loaded normotensive rats.

	Dose mg kg^{-1}, p.o.	Control	+2 h	+4 h	+6 h	n
Saline		113±4·4	115±2·7	110±0·8	111±3·8	7
Hydralazine	0·316	108±8·4	113±8·4	108±9·2	112±10·1	4
	3·16	107±4·8	81±3·3*	78±3·6*	86±2·1	4
	31·6	108±2·6	71±0·8*	69±4·2*	63±2·8*	4
Nifedipine	0·316	111±3·7	116±6·0	119±9·2	119±6·0	4
	3·16	120±5·2	110±2·6	106±6·4	106±6·0	4
	31·6	109±1·9	84±2·7*	84±2·4*	90±3·3*	4
Nitrendipine	0·316	107±5·9	105±3·3	104±3·9	105±8·0	4
	3·16	131±5·8	130±6·8	121±8·0	128±4·1	4
	31·6	112±5·7	81±6·1*	83±5·4*	87±8·9	4
Nimodipine	0·316	118±5·3	124±6·7	119±6·9	118±9·4	4
	3·16	105±4·0	107±6·3	110±9·2	116±8·5	4
	31·6	123±8·2	99±6·2	86±8·1*	93±10·0	4
Cinnarizine	0·316	103±7·0	110±6·4	99±4·5	106±7·4	4
	3·16	106±6·8	115±2·4	104±6·2	105±8·6	4
	31·6	117±10·0	116±7·9	117±12·1	110±11·0	4
	100·0	114±4·2	117±4·1	122±6·3	121±2·3	4
Flunarizine	0·316	108±4·6	114±1·7	105±6·3	111±10·6	4
	3·16	120±6·3	114±2·7	108±4·7	108±5·1	6
	31·6	98±5·0	90±4·3	94±2·6	97±2·5	5
	100·0	101±2·2	79±3·4*	84±5·3*	89±3·9	5
Prenylamine	0·316	106±6·0	120±9·8	110±7·4	105±6·4	4
	3·16	116±6·0	116±4·7	106±5·1	105±4·2	4
	31·6	98±6·3	105±8·4	100±8·8	102±9·4	6
	100·0	118±2·7	116±3·8	114±11·6	107±8·2	4
Diltiazem	0·316	109±8·9	119±6·6	115±6·2	109±4·9	6
	3·16	110±11·3	118±12·0	119±15·3	123±9·1	4
	31·6	110±7·6	103±5·6	102±5·2	107±5·8	6
	100·0	117±6·6	90±5·0*	92±4·9*	96±5·3*	4
Verapamil	0·316	102±3·7	105±1·3	97±9·9	102±16·5	4
	3·16	100±6·4	110±1·9	106±4·6	107±2·7	4
	31·6	109±4·5	78±2·4*	84±2·3*	88±2·9*	4

* $P < 0·05$; Dunnett's test, n as indicated.

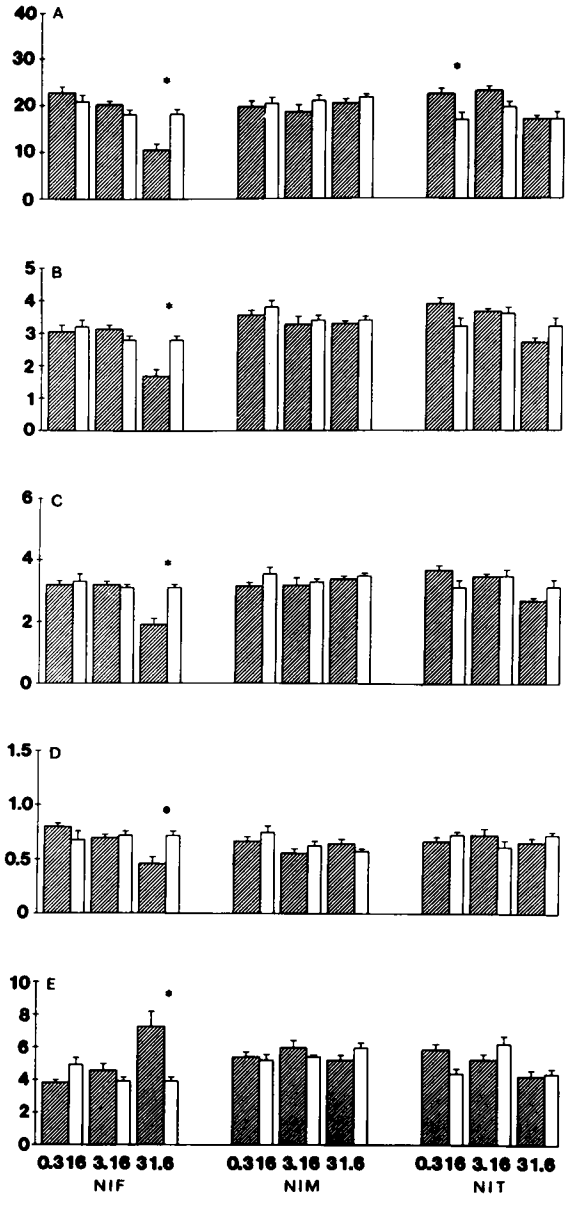

FIG. 2. Urine and electrolyte excretory profile in rats treated with saline (open bars), nifedipine (NIF), nimodipine (NIM), or nitrendipine (NIT) (shaded bars). n = 2 per cage, 5–6 cages per group. Doses as indicated below each bar. • = $P < 0.05$. Key as Fig. 1.

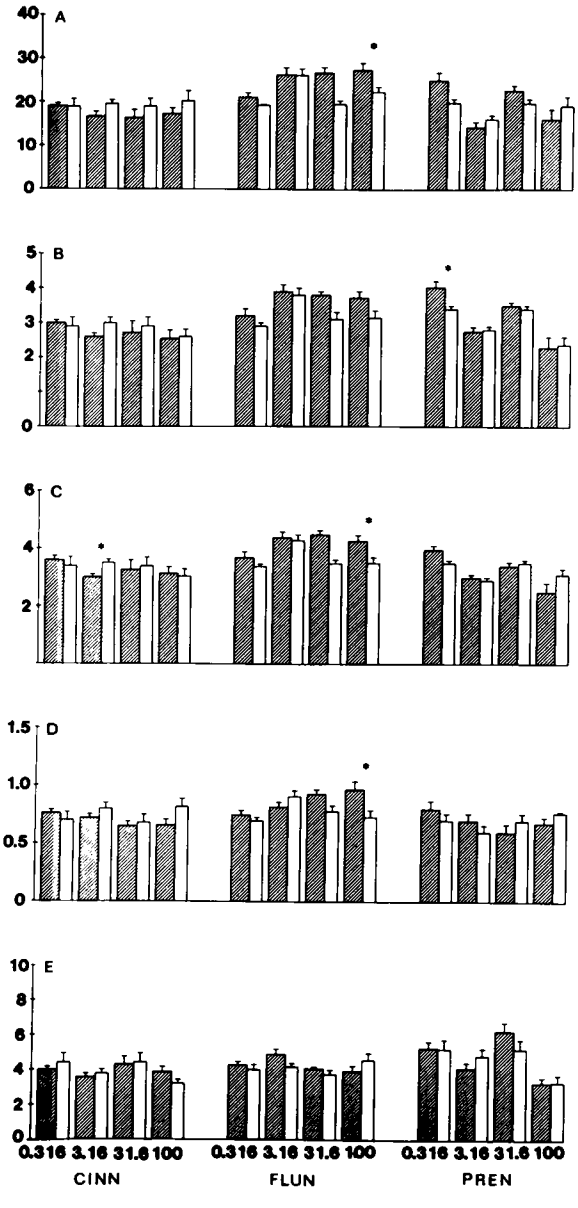

FIG. 3. Excretion of urine and electrolytes in rats treated with saline (open bars), flunarizine (FLUN), cinnarizine (CINN), or prenylamine (PREN) (shaded bars). n = 2 per cage, 5–6 cages per group, except 100 mg kg^{-1} flunarizine: n = 10. Doses as indicated below each bar. • = $P < 0.05$. Key as Fig. 1.

treatment with 100 mg kg^{-1} flunarizine, in spite of a marked drug-induced decrease in MABP (Table 1).

Prenylamine produced a slight natriuretic response in rats treated with 0·316 mg kg^{-1}, but not in those treated with the higher doses (Fig. 3). None of the doses tested affected MABP (Table 1).

The two lower doses of diltiazem (0·316 and 3·16 mg kg^{-1}) had no discernable effect on urine and electrolyte excretion nor on MABP. However, animals treated with 31·6 and 100 mg kg^{-1} diltiazem displayed dose-related enhancement of urine, Na^+, K^+, and Cl^- excretion (Fig. 4). MABP was unchanged in animals treated with 31·6 mg kg^{-1}, but the 100 mg kg^{-1} dose of diltiazem provoked saluresis in spite of a marked hypotensive effect (Table 1).

Verapamil caused only minimal variations from control renal excretory patterns (Fig. 4), the only significant alteration being a modest and isolated antikaliuresis following treatment with 31·6 mg/kg^{-1}, a dose which produced hypotension (Table 1). The lower doses tested failed to influence resting MABP.

Table 2 summarizes the similarities and differences in the cardiovascular and renal responses evoked by the Ca^{2+} channel blockers. Two drugs, nitrendipine and prenylamine, slightly enhanced diuresis without altering MABP. In spite of drug-induced reductions in MABP similar to those caused by hydralazine, flunarizine and diltiazem evoked diuretic responses; while nimodipine, nitrendipine, and verapamil each failed to trigger the antidiuretic and electrolyte-retaining responses observed in hydralazine-treated animals. Only nifedipine provoked such a response.

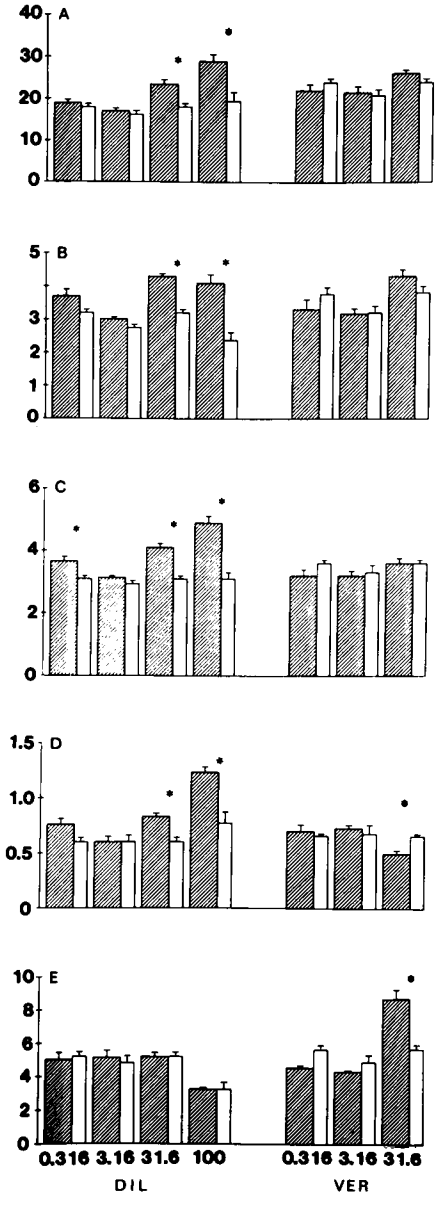

FIG. 4. Excretion of urine and electrolytes in rats treated with saline (open bars), diltiazem (DIL), or verapamil (VER) (shaded bars). n = 2 per cage, 5–6 cages per group. Doses as indicated below each bar. * = $P < 0.05$. Key as Fig. 1.

Discussion

These studies were conducted to determine if a particular compound or chemical subgroup of Ca^{2+} channel blockers evoked relatively greater diuretic activity or a unique pattern of urinary electrolyte excretion. Previous studies have reported that selected Ca^{2+} channel blockers have produced diuresis, antidiuresis, or no effect; the results of the experiments reported here are in accord with some studies, but do not confirm others. The discrepancies in earlier reports may be due to differences in experimental designs (hydration, anaesthesia, species, strains, etc.). Because of the variability in methods used, it has heretofore been impossible to validly compare renal responses to the Ca^{2+} channel blockers. In the present studies, all compounds were examined under identical conditions, thus facilitating a valid comparison of the renal actions of both individual drugs and chemical subgroups.

To provide a basis for qualitative and quantitative comparison of the effects of the Ca^{2+} channel blockers on diuresis and electrolyte excretion, a vasodilator and two pharmacologically distinct diuretics were tested in parallel with the test compounds. Hydrochlorothiazide and amiloride enhanced excretion of urine, Na^+, and Cl^-, and produced predictable divergent effects on K^+ excretion. Hydralazine produced expected dose-related antidiuretic and electrolyte-retaining responses which are known to occur secondarily to systemic vasodilation (Koch-Weser 1979; Gross 1977; Garthoff et al 1983). In addition to providing standards for comparison, these results confirmed the reliability and sensitivity of the model system to detect a variety of drug effects.

Of all the Ca^{2+} channel blockers tested, only diltiazem and flunarizine were clearly diuretic, and diltiazem was the only agent to display dose-dependency. Although obviously saluretic, the maximal responses observed in animals treated with diltiazem or flunarizine were less than those produced by low doses of hydrochlorothiazide or amiloride under the same conditions. Their diuretic activity would therefore be classified as very weak. The slight responses evoked by the low doses of prenylamine and nitrendipine suggest that they too may be weakly diuretic.

Table 2. Summary of statistically significant ($P < 0.05$) diuretic/natriuretic and hypotensive responses observed following treatment with hydralazine or Ca^{2+} channel blockers.

Drug dose (mg kg^{-1} p.o.)		Change from control MABP mmHg	%	Renal response
Hydralazine,	3·16	−26	−24·3	Retention
Hydralazine,	31·6	−39	−34·3	Retention
Nifedipine,	31·6	−25	−22·9	Retention
Nimodipine	31·6	−37	−30·1	No change
Nitrendipine,	31·6	−31	−27·7	No change
Verapamil,	31·6	−31	−28·4	No change
Flunarizine,	100·0	−22	−21·8	Diuresis
Diltiazem,	31·6	No change		Diuresis
Diltiazem,	100·0	−27	−23·1	Diuresis
Nitrendipine,	0·316	No change		Diuresis
Prenylamine,	0·316	No change		Diuresis

Since urine and electrolyte excretion were enhanced by a benzothiazepine (diltiazem), a diphenylpiperazine (flunarizine), a phenylalkylamine (prenylamine), and a dihydropyridine (nitrendipine), it is apparent that this renal pharmacological activity was not restricted to a particular chemical class of Ca^{2+} channel blocker. Nor was activity dependent upon the presence of a particular structural moiety, such as is the case with the sulfamoyl group on the benzothiadiazine diuretics.

Earlier studies reported that the dihydropyridines felodipine (DiBona & Sawin 1984; Edgar et al 1985), nitrendipine, and nifedipine (Ene et al 1985; Zanchetti & Leonetti 1985) increased urinary Na^+ excretion, but neither spared nor wasted K^+. Such a profile would represent a truly unique diuretic that would have considerable therapeutic benefit over those currently available. In view of the potential importance of such a finding, the effects on the ratio of Na^+ to K^+ excretion of not only the dihydropyridines, but also several other structurally distinct Ca^{2+} channel blockers were carefully scrutinized. Unfortunately, the only compounds that evoked significant diuresis—diltiazem, flunarizine, prenylamine, and nitrendipine—produced nearly equivalent natriuresis and kaliuresis; the Na/K ratios remained unaltered. (Nitrendipine tended to excrete more Na^+ than K^+, but the drug's effects on both ions were minimal and were not dose-related.) Thus, under controlled conditions sensitive to changes in K^+ excretion, none of the Ca^{2+} channel blockers tested showed evidence for a K^+-sparing or isokaliuretic diuretic action.

As indicated in the introduction, it was not the intention of this study to evaluate the overall cardiovascular and renal functional effects of each of these agents. Indeed, extensive studies far beyond the objectives and scope of this report would be required to identify the systemic and intrarenal haemodynamic, neuronal, and humoral components of the renal excretory responses to each drug. However, because Ca^{2+} channel blockers as a class are known vasodilators, and vasodilators typically produce urine and electrolyte retention, it was of particular interest to determine if any observed diuretic responses were associated with, or were separable from, drug-induced alterations in blood pressure.

The principal difference between the hypotensive and renal responses to hydralazine and the Ca^{2+} channel blockers lies in the association of water and electrolyte retention with vasodepression following hydralazine, and the nearly absolute dissociation of these effects after Ca^{2+} channel blocker treatment. Only nifedipine caused urinary and electrolyte retention, although several compounds produced equivalent hypotensive responses. The dihydropyridines nimodipine and nitrendipine, and the structurally dissimilar flunarizine, diltiazem, and verapamil each reduced MABP by a magnitude similar to that produced by hydralazine or nifedipine (21–30% below control). However, diltiazem and flunarizine were clearly diuretic, while nimodipine, nitrendipine, and verapamil neither enhanced nor limited urine and electrolyte excretion. Lower doses of diltiazem, flunarizine, and nitrendipine produced diuresis without affecting MABP. These results suggest that the diuretic and vasodepressor responses to these drugs are separable. However, it is possible that intrinsic diuretic activty of the Ca^{2+} channel blockers and the antidiuretic renal counter-regulatory mechanisms triggered by hypotension may oppose one another. Further studies must determine whether Ca^{2+} channel blockers attenuate renal compensatory antidiuresis by intrinsic diuretic activity, or by interference with activation of the counter-regulatory mechanisms.

Ca^{2+} channel blockers have been shown to interfere with virtually every renal and extrarenal system involved with the regulation of physiological fluid and electrolyte balance. Diuresis or impaired renal compensation to hypotension may be caused by alterations of renal and glomerular haemodynamics (Ono et al 1974; Garthoff et al 1983; Bell & Lindner 1984; Loutzenhiser & Epstein 1985; Zanchetti & Leonetti 1985), inhibition of tubular ionic reabsorptive mechanisms (DiBona & Sawin 1984; Zanchetti & Leonetti 1985), and/or reduced activity of the renin-angiotensin-aldosterone axis (Ichikawa et al 1979; Garthoff et al 1983; Bell & Lindner, 1984; Rosenkrantz et al 1984). Determination of the relative involvement of each of these factors in the renal responses to the various Ca^{2+} channel blockers is clearly needed.

The renal excretory and blood pressure studies were performed under similar conditions in saline-loaded, conscious, normotensive rats, but they were not conducted simultaneously in the same animals. It must be considered that the observed relationships between the measured parameters may not apply as precisely as they might had all measurements been taken from the same animals. However, our experience is that both experimental systems are extremely sensitive, reliable, and consistently provide data with minimal variance. Thus they may be related to one another with a considerable degree of confidence.

In summary, although diltiazem produced relatively greater diuretic and natriuretic actions than the other Ca^{2+} channel blockers tested, renal pharmacological activity was not restricted to, nor absent from, a particular structural class. When responses were observed, they were weaker than those produced by known diuretics; no evidence of a K^+-sparing or isokaliuretic effect was observed. Unlike the responses to other vasodilators, hypotensive responses to the Ca^{2+} channel blockers were generally dissociated from water and electrolyte retention.

Acknowledgements

The authors wish to thank the pharmaceutical firms for the drugs used, Martha Hampton for assistance in the preparation of the manuscript, and Barbara Allen for reproducing the figures.

References

Ames, R. P. (1983) Negative effects of diuretic drugs on metabolism risk factors for coronary heart disease: possible alternative drug therapies. Am. J. Cardiol. 55: 632–638

Bell, A. J., Lindner, A. (1984) Effects of verapamil and nifedipine on renal function and hemodynamics in the dog. Renal Physiol. 7: 329–343

Brunn, N. E., Ibsen, H., Nielsen, F., Nielsen, M. D., Moelbak, A.-G., Hartling, O. J. (1986) Lack of effect of nifedipine on counterregulatory mechanisms in essential hypertension. Hypertension 8: 655–661

Burke, T. J., Arnold, P. E., Gordon, J. A., Bulger, R. E., Dobyan, D. C., Schrier, R. W. (1984) Protective effect of intrarenal calcium membrane blockers before or after renal ischemia. J. Clin. Invest. 74: 1830–1841

DiBona, G. F., Sawin, L. L. (1984) Renal tubular site of action of felodipine. J. Pharmacol. Exp. Ther. 228: 420–424.

Dunnett, C. W. (1955) A multiple comparisons procedure for comparing several treatments with a control. J. Am. Stat. Assoc. 50: 1096–1121

Edgar, B., Bengtsson, B., Elmfeldt, D., Lundborg, P., Nyberg, G., Raner, S., Rann, O. (1985) Acute diuretic/natriuretic properties of felodipine in man. Drugs 29 Suppl. 2: 176–184

Ene, M. D., Williamson, P. J., Roberts, C. J. C., Waddell, G. (1985) The natriuresis following oral administration of the calcium antagonists—nifedipine and nitrendipine. Br. J. Clin. Pharmacol. 19: 423–427

Garthoff, B., Knorr, A., Thomas, G., Kazda, S. (1982) Mitrendipine increases sodium excretion in acutely saline-loaded rats. Biochem. Pharmacol. 31: 3015–3016

Garthoff, B., Kazda, S., Knorr, A., Thomas, G. (1983) Factors involved in the antihypertensive action of calcium antagonists. Hypertension 5 Suppl. II: II–34–38

Gross, F. (1977) in: Gross, F. (ed.) Drugs acting on arteriolar smooth muscle (vasodilator drugs). In: Gross F. (ed) Antihypertensive Agents. Springer-Verlag, Berlin, pp. 397–476

Ichikawa, I., Miele, J. F., Brenner, B. M. (1979) Reveral of renal cortical actions of angiotensin II by verapamil and manganese. Kidney Int. 16: 137–147

Janis, R. A., Scriabine, A. (1983) Sites of action of Ca^{++} channel inhibitors. Biochem. Pharmacol. 32: 3499–3507

Johns, E. J., (1985) The influence of diltiazem and nifedipine on renal function in the rat. Brit. J. Pharmacol. 84: 707–713

Kau, S. T., Keddie, J. R., Andrew, D. (1984) A method for screening diuretic agents in the rat. J. Pharmacol. Meth. 11: 67–75

Koch-Weser, J. (1979) Vasodilator drugs in treatment of hypertension. Arch. Intern. Med. 133: 1017–1019

Lipschitz, W. L., Hadidian, Z., Kerpscar, A. (1943) Bioassay of diuretics. ٢. Pharmacol. Exp. Ther. 79: 97–110

Loutzenhiser, R., Epstein, M. (1985) Effects of calcium antagonists on renal hemodynamics. Am. J. Physiol. 249: F619–629

MacLaughlin, M., deMello Aires, M., Malnic, G. (1985) Verapamil effect on renal function of normotensive and hypertensive rats. Renal Physiol. 8: 112–119

Malis, C. D., Cheung, J. Y., Leaf, A., Bonaventre, J. V. (1983) Effects of verapamil in models of acute renal failure in the rat. Am. J. Physiol. 245: F735–742

Millard, R. W., Lathrop, D. A., Grupp, G., Ashraf, M., Grupp, I. L., Schwartz, A. (1982) Differential cardiovascular effects of calcium channel blocking agents: potential mechanisms. Am. J. Cardiol. 49: 499–506

Nagao, T., Yamaguchi, I., Narita, H., Nakajima, H. (1985) Calcium entry blockers: antihypertensive and natriuretic effects in experimental animals. Am. J. Cardiol. 56: 56–61H

Narita, H., Nagao, T., Yabana, H., Yamaguchi, I. (1983) Hypotensive and diuretic actions of diltiazem in spontaneously hypertensive and Wistar Kyoto rats. J. Pharmacol. Exp. Ther. 227: 472–477

Ono, H., Kokubun, H., Hashimoto, K. (1974) Abolition by calcium antagonists of autoregulation of renal blood flow. Naunyn-Schmiedeberg's Arch. Pharmacol. 285: 201–207.

Rosenkranz, R. P., McClelland, D. L., Roszkowski, A. P. (1984) Effects of nicardipine, nifedipine, verapamil, and diltiazem on urine volume, sodium, and potassium excretion and plasma aldoterone levels in the rat. Proc. West. Pharmacol. Soc. 27: 67–72.

Wait, R. B., White, G., Davis, J. H. (1983) Beneficial effects of verapamil on post-ischemic renal failure. Surgery 94: 276–282

Zanchetti, A., Leonetti, G. (1985) Natriuretic effect of calcium antagonists. J. Cardiovasc. Pharmacol. 7 Suppl. 4: S33–37