Amlodipine and haemodynamic effects of cyclo-oxygenase inhibition

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- 1 The haemodynamic effects of calcium antagonists could depend at least in part on the activity of vasoactive prostanoids.
- 2 We set out to study the effect of the cyclo-oxygenase inhibitor ibuprofen, 400 mg three times daily for 3 days, by a randomised cross-over study *vs* placebo in 12 mild to moderate essential hypertensive patients who had been treated for 1 month with amlodipine.
- 3 Blood pressure, heart rate and vascular resistances in the upper limb (Doppler ultrasound) were measured. Plasma renin activity and urinary aldosterone, as well as indices of renal function, were evaluated. Urinary 2,3-dinor-6-keto-PGF_{1α} and 2,3-dinor-TXB₂, as well as 6-keto-PGF_{1α} and TXB₂, were measured as indices of systemic and renal PGI₂ and TXA₂ synthesis.
- 4 Amlodipine normalised blood pressure and reduced upper limb vascular resistances; it did not affect urinary prostanoid excretion. Short-term combined administration of ibuprofen resulted in, by comparison with placebo, inhibition of systemic PGI₂ (−80.5 ng 24 h^{−1}, 95% CI −99.2, −61.4; *P* < 0.001) and TXA₂ (−216.1 ng 24 h^{−1}, 95% CI −276.5, −155.8; *P* < 0.001), together with an increase in systolic (+7.8 mm Hg, 95% CI +3.1, +12.3; *P* < 0.01) and diastolic (+3.9 mm Hg, 95% CI +1.2, +6.6; *P* < 0.01) blood pressure; it had no significant effect on regional vascular resistances (+4.7 mm Hg ml^{−1} s, 95% CI −5.6, +15.0). Effects of ibuprofen on renal prostanoid synthesis were less marked, and there was no change in indices of renal function or hydro-electrolytic balance.
- 5 The haemodynamic effects of amlodipine may be partially antagonised by ibuprofen, which mainly determines inhibition of extrarenal prostanoid synthesis. It is suggested that this antagonism is attributable not so much to a direct effect of the calcium antagonist on prostacyclin synthesis as to an alteration in vascular tone, dependent on prostacyclin and perhaps other vasodilatory prostanoids.

Keywords amlodipine ibuprofen cyclo-oxygenase inhibitors human hypertension
haemodynamics arterial resistances prostacyclin thromboxane

Introduction

The antihypertensive action of calcium antagonists is essentially based on blockade of voltage-dependent calcium channels in vascular smooth muscle, which leads to uncoupling of excitation and contraction. These events result in generalised arterial and venous dilation [1]. *In vivo*, calcium antagonists can also promote diuresis, mainly by modifications of renal haemodynamics [2, 3].

It has been suggested that activation of endogenous vasodilatory factors such as prostacyclin could con-

tribute to the overall haemodynamic effects of calcium antagonists [4] and to their inhibitory action on platelet aggregation and atherogenesis [5]. Studies in man to date have not proved conclusive in this respect.

To evaluate the hypothesis that prostacyclin or other vasoactive prostanoids may contribute to the antihypertensive effect of calcium antagonists, we studied the haemodynamic effects of short-term administration of a specific cyclo-oxygenase inhibitor in

essential hypertensives receiving amlodipine, a long-acting dihydropyridine calcium antagonist [6].

We also sought to identify the mechanism by which the prostanoids may have exerted any haemodynamic effects. Inhibition of renal prostaglandin synthesis may lead, in man, to sodium and water retention, and thus to elevation of blood pressure [7]. Experimentally, vasoconstriction of systemic vessels has also been observed after administration of non-steroidal anti-inflammatory drugs (NSAIDs)—a mechanism which could intrinsically be prohypertensive [8]. We therefore measured some indices of renal function and water-electrolyte balance, as well as studying arterial haemodynamics and determining parameters of musculo-cutaneous vascular resistance in the upper limb.

Methods

Study protocol

The study was a single-blind, cross-over comparison with placebo in mild-to-moderate essential hypertensive patients. The duration of the study for each patient was about 70 days, subdivided into a wash-out period of at least 21 days without any drug treatment and 46 days' therapy with amlodipine. In combination with this regimen, patients were allocated by simple randomisation to additional treatment with ibuprofen or placebo on days 31–33, followed by cross-over on days 44–46.

Patients were examined on five different occasions.

At the end of the wash-out period (day 0), 24 h urine collection was performed for determination of urinary prostanoids, sodium, potassium, chloride and creatinine. On day 1 of the study, generally at 09.00 h, patients underwent non-invasive haemodynamic study. Blood pressure and heart rate were measured, as were flow velocity and local vascular resistances of the right arm. Finally, a blood sample was taken to evaluate plasma renin activity (PRA) and plasma creatinine, electrolytes and albumin.

Amlodipine 10 mg once daily was then administered for 30 days. On day 30, 2 h after treatment, the parameters included in the basal examination were again evaluated. For the next 3 days, amlodipine was combined with thrice-daily oral administration of ibuprofen 400 mg or placebo, prior to a further evaluation of the above parameters. Amlodipine alone was then administered until day 43, when the study parameters were again evaluated prior to cross-over with ibuprofen or placebo for 3 days. This was followed by one final evaluation on day 46.

The persons who performed haemodynamic and laboratory measurements did not know the randomisation sequence.

Patients

Twelve male outpatients, aged 40–59 years, were recruited following diagnosis of mild or moderate hypertension (mean diastolic blood pressure = 95–

105 mm Hg for three successive measurements, after 15 min in the supine position). Uncomplicated essential hypertension was confirmed by standard clinical criteria (negative renal arteriography or scintigraphy in many subjects). All patients were subjected at the time of recruitment to objective examination, anamnesis, biochemical analyses and ECG.

Criteria for exclusion were: previous severe hypertension or history of cardiovascular disease, renal insufficiency (plasma creatinine $> 115 \mu\text{mol l}^{-1}$), and any other major disease. Patients with a history of hypersensitivity to or intolerance of NSAIDs or calcium antagonists were also excluded. Informed consent was obtained in all cases. No patient had to discontinue the treatment because of side effects of the drugs.

Method of local haemodynamic evaluation

All haemodynamic evaluations were performed between 09.00 h and 10.00 h, in a comfortable environment at a constant temperature of $21 \pm 1^\circ \text{C}$, after overnight fasting and at least 15 min rest in a supine position.

Supine blood pressure and heart rate were measured automatically, using an oscillometric method (Dinamap 845 XT, Criticon, Tampa, FL, USA), every 2 min throughout the examination. Using a high resolution Duplex scanner with a 10 MHz probe (Diasonics CV400, Diasonics, Milpitas, CA, USA), brachial artery blood flow volume was measured (variability coefficient g%). Forearm vascular resistances, calculated as the ratio between mean blood pressure and blood flow volume, were expressed in $\text{mm Hg ml}^{-1} \text{s}$ [9].

Method for determining urinary prostanoids

As indices of PGI_2 and TXA_2 synthesis, we determined urinary excretion of their catabolites. Urinary 2-3-dinor TXB_2 and 2-3-dinor-6-keto- $\text{PGF}_{1\alpha}$ as products of PGI_2 and TXA_2 β -oxidation, are considered indices of systemic PGI_2 and TXA_2 production, while the main source of 6-keto- $\text{PGF}_{1\alpha}$ and TXB_2 deriving from the spontaneous hydrolysis of PGI_2 and TXA_2 in the urine is normally the kidney [10]. Since patients were male, they were asked to abstain from sex in the days prior to urine collection, with a view to minimising any passage of prostanoids from the lower urogenital tract.

Urinary prostanoids were determined by radioimmunoassay (r.i.a.). Dinor metabolites of PGI_2 and TXA_2 were separated from 6-keto- $\text{PGF}_{1\alpha}$ and TXB_2 by h.p.l.c. as described previously [11]. R.i.a. was performed with commercial anti- TXB_2 (Biomol, Plymouth, PA, USA) and 6-keto- $\text{PGF}_{1\alpha}$ (Cayman, Ann Arbor, MI, USA) antisera. Using the same antisera, we also assayed the dinor-derivatives of TXB_2 and 6-keto- $\text{PGF}_{1\alpha}$, with which the respective antibodies showed high cross-reactivity (roughly 100%). Tritium-labelled TXB_2 and 6-keto- $\text{PGF}_{1\alpha}$ used were supplied by Amersham Co., Amersham UK. Non-labelled 2,3-dinor-6-keto- $\text{PGF}_{1\alpha}$ and 2,3-dinor- TXB_2 used as reference standards were supplied by Cayman

Co., Ann Arbor, MI, USA. Inter- and intra-assay variability for r.i.a. were < 9% and < 14%, respectively.

Sodium, potassium, chloride and creatinine were determined by automatic analysis (Dax 96, Technicon). Plasma renin activity (PRA) and urinary aldosterone were assayed by r.i.a. (Serono Biodata SpA, Roma, Italy).

Statistical analysis

Statistical analysis of the ibuprofen-placebo comparison was carried out according to the recommendations of Hills & Armitage for two-period cross-over studies. Using these methods of analysis, any period effect and treatment-period interaction were evaluated [12]. Results were analysed by parametric testing (Student's *t*-test). When normal distribution of data could not be identified, as for vascular resistance, non-parametric tests were also used (Wilcoxon's rank test). Values of *P* < 0.05 were considered statistically significant. Data are presented as mean and s.d. Mean values with 95% confidence intervals for the differences between placebo and ibuprofen are also provided for the main study end-points.

Results

After 30 days' amlodipine, systolic and diastolic blood pressure showed a significant reduction, returning within the normal range; local vascular resistances were markedly reduced; and PRA, together with plasma and urinary creatinine, remained unchanged (Figure 1 and Table 1).

A further reduction in regional vascular resistances was observed after 43 days' treatment (after the 10 day period with amlodipine alone (Table 1).

No effect of amlodipine on urinary prostanoids was observed after 30 days' treatment, and there was a slight increase in urinary 2,3-dinor-TXB₂ after 43 days (Table 1).

Following combined amlodipine-ibuprofen, there was a significant increase, compared with placebo, of 7.8 mm Hg (95% CI +3.1, +12.3) in systolic and 3.9 mm Hg (95% CI +1.2, +6.6) in diastolic blood pressure (Table 2 and Figure 1). No increase was observed in local vascular resistances (+4.7 mm Hg ml⁻¹ s, 95% CI -5.6, +15.0) (Figure 1 and Table 3).

Ibuprofen also inhibited prostaglandin synthesis, with marked reduction in urinary 2,3-dinor-6-keto-

Figure 1 Effects of ibuprofen (▨) and placebo (□) on systolic and diastolic blood pressure and vascular resistance. ** = *P* < 0.01 for differences between groups. Data are expressed as mean ± s.e. mean.

Table 1 Effects of amlodipine on systolic (SBP) and diastolic (DBP) blood pressure, vascular resistance of the upper limb (R), plasma renin activity, creatinine, urinary aldosterone and prostanoid excretion. Data for pre-treatment period (Basal) and for 30th and 43rd day of treatment with amlodipine, i.e. basal values before randomisation to ibuprofen or placebo. Data are expressed as mean and s.d.

	Basal	30 days	43 days
SBP (mm Hg)	160.6 ± 11.5	138.3 ± 6.5	136.5 ± 8.2
DBP (mm Hg)	100.2 ± 4.0	85.9 ± 4.5	85.3 ± 5.0
R (mm Hg ml ⁻¹ s)	116.1 ± 74.6	61.8 ± 32.0	47.6 ± 27.3
HR (beats min ⁻¹)	66.1 ± 7.6	65.7 ± 8.1	65.4 ± 7.2
Plasma renin activity (ng ml ⁻¹ h ⁻¹)	0.95 ± 1.02	1.63 ± 1.38	1.73 ± 1.73
Plasma creatinine (μmol l ⁻¹)	98.2 ± 7.9	100.8 ± 7.1	99.9 ± 7.1
Urinary creatinine (mmol 24 h ⁻¹)	130.9 ± 26.5	131.8 ± 44.2	130.0 ± 35.4
Urinary aldosterone (μg 24 h ⁻¹)	11.5 ± 5.9	12.6 ± 4.7	15.3 ± 6.1
6-keto-PGF _{1α} (ng 24 h ⁻¹)	65.7 ± 35.9	60.2 ± 25.8	76.6 ± 46.2
TXB ₂ (ng 24 h ⁻¹)	150.1 ± 169.2	129.8 ± 72.0	132.8 ± 49.7
dn6-keto-PGF _{1α} (ng 24 h ⁻¹)	106.2 ± 51.6	97.0 ± 61.7	146.4 ± 88.9
dnTXB ₂ (ng 24 h ⁻¹)	253.7 ± 144.8	300.2 ± 108.6	357.7 ± 132.7

Table 2 Effects of ibuprofen, compared with placebo, on systolic blood pressure and diastolic blood pressure. Individual values and mean $\pm$ s.d. for the two treatment groups to which patients were randomly allocated. The table also indicates the mean difference in blood pressure observed in each group

Systolic blood pressure (mm Hg)			Diastolic blood pressure (mm Hg)		
Ibuprofen	Placebo	Difference	Ibuprofen	Placebo	Difference
Group A (ibuprofen/placebo)					
134	132		87	82	
138	135		88	85	
140	143		86	87	
130	130		91	90	
136	132		84	85	
135.6	134.4	1.2	87.2	85.8	1.4
± 3.9	± 5.1	± 2.8	± 2.6	± 2.9	± 2.3
Group B (placebo/ibuprofen)					
160	140		100	90	
148	132		96	85	
157	146		90	88	
138	132		79	78	
132	125		80	80	
145	128		90	80	
150	140		90	86	
147.1	134.7	12.4	89.3	83.9	5.4
± 9.9	± 7.5	± 5.3	± 7.7	± 4.6	± 4.8

Table 3 Effects of ibuprofen, compared with placebo, on vascular resistance of the upper limb. Individual values and mean $\pm$ s.d. for the two treatment groups to which patients were randomly allocated. The table also indicates the mean difference in vascular resistance observed in each group

Vascular resistance (mm Hg ml ⁻¹ s)		
Ibuprofen	Placebo	Difference
Group A (ibuprofen/placebo)		
84.6	79.2	
52.1	55.1	
73.4	50.8	
41.3	24.6	
58.3	73.9	
61.9 $\pm$ 17.2	56.7 $\pm$ 21.6	5.2 $\pm$ 15.3
Group B (placebo/ibuprofen)		
55.7	45.1	
157.6	134.6	
42.8	45.1	
97.2	125.2	
31.9	26.8	
76.2	51.4	
18.3	20.5	
68.5 $\pm$ 47.4	64.1 $\pm$ 46.3	4.4 $\pm$ 17.9

PGF_{1 α} (-80.5 ng 24 h⁻¹, 95% CI -99.2 , -61.4) and 2,3-dinor-TXB₂ (-216 ng 24 h⁻¹, 95% CI -276.5 , -155.8). There was a less marked effect on urinary 6-keto-PGF_{1 α} (-24.6 ng 24 h⁻¹, 95% CI -44.9 , -4.6) and TXB₂ (-37.6 ng 24 h⁻¹, 95% CI -57.6 , -17.6), indices of renal PGI₂ and TXA₂ synthesis (Figure 2).

A period effect was observed only for systolic blood pressure, higher when ibuprofen was admin-

Figure 2 Effects of ibuprofen (▨) and placebo (□) on urinary excretion of PGI₂ and TXA₂ metabolites. * = $P < 0.05$, *** = $P < 0.001$ for differences between the groups. Data are expressed as mean $\pm$ s.e. mean.

istered during the second study period (Table 2). No treatment-period interaction was observed for any of the study parameters.

During treatment with ibuprofen, there was no change in urinary aldosterone and creatinine, or PRA and plasma creatinine (Table 4).

Throughout the study, there were no changes in urinary sodium, potassium or volume. Plasma albumin, sodium and potassium also remained unchanged (Tables 1 and 4).

Discussion

In this study, amlodipine showed a clear antihypertensive effect and improved haemodynamics, determining reduction of peripheral resistances in the forearm. There have been other reports of dihydropy-

Table 4 Effects of amlodipine plus either ibuprofen or placebo on heart rate (HR), plasma renin activity, creatinine, plasma albumin, urinary aldosterone and electrolytes. Data are expressed as mean and s.d.

	Amlodipine + placebo	Amlodipine + ibuprofen
HR (beats min ⁻¹)	65.6 ± 7.1	65.8 ± 7.8
Plasma renin activity (ng ml ⁻¹ h ⁻¹)	1.3 ± 0.7	1.07 ± 0.7
Plasma creatinine (μmol l ⁻¹)	98.2 ± 8.0	101.7 ± 8.8
Plasma albumin (g l ⁻¹)	49.0 ± 2.5	48.8 ± 1.5
Urinary creatinine (mmol 24 h ⁻¹)	138.9 ± 51.4	122.9 ± 53.1
Urinary aldosterone (μg 24 h ⁻¹)	14.7 ± 4.9	12.7 ± 7.4
Urinary Na (mmol 24 h ⁻¹)	142.3 ± 70.7	145.9 ± 70.0
Urinary K (mmol 24 h ⁻¹)	63.1 ± 23.7	54.5 ± 26.8
Urinary Cl (mmol 24 h ⁻¹)	149.9 ± 74.3	158.3 ± 70.6

ridine calcium antagonists reducing peripheral resistance [13] and thus showing that they are active on the musculature of the smaller vessels which are most involved. The treatment period in the present study, while relatively brief, was sufficient to determine a stable hypotensive response, though a change in the effect of treatment on blood pressure could be responsible for the period effect in subjects evaluated during ibuprofen administration. The overall haemodynamic effect of amlodipine is thus attributable to reduction in arterial tone and in vascular reactivity to prohypertensive stimuli [14].

While amlodipine alone did not affect urinary excretion of prostaglandin metabolites, its antihypertensive effect was at least partly antagonised by ibuprofen-induced inhibition of cyclo-oxygenase.

Brief courses of treatment with NSAIDs can increase blood pressure and reduce the efficacy of many antihypertensives administered chronically [7], particularly β -adrenoceptor blockers and diuretics [15, 16]. Evidence of effects on the efficacy of ACE inhibitors [17] is more limited.

Current data on the effects of prostaglandin synthesis inhibition on the activity of calcium antagonists are limited [5, 7, 18]. A lack of change in blood pressure after 1 week of treatment with indomethacin in patients receiving nifedipine was regarded as evidence that the prostaglandin system is not involved in the vasodilatory and antihypertensive activity of nifedipine [19].

The different results of the present study could depend in part on the different degree of inhibition of vasodilatory prostaglandin synthesis determined by different drugs administered for various periods, as well as on differences in the pharmacokinetics of nifedipine and amlodipine.

To evaluate the overall effect of ibuprofen on prostanoid production, we used a specific assay which allowed a parallel analysis of urinary metabolites of prostacyclin and thromboxane. Since the metabolic pathways leading to the formation of 6-keto-PGF_{1 α} and its dinor derivative are in part different, we were also able to gain an idea of where prostacyclin synthesis takes place.

The prohypertensive effect of NSAIDs has, in fact, been considered primarily dependent on inhibition

of renal prostacyclin synthesis [7, 20]. Renal cyclo-oxygenase inhibition could affect intrarenal haemodynamics, promoting water and sodium retention. NSAIDs which exert little effect on renal cyclo-oxygenase would thus not affect blood pressure [21].

NSAIDs could, however, also increase blood pressure by causing vasoconstriction in other regions of the systemic circulation. Prostacyclin—perhaps together with other prostaglandins like PGE₂ in the small vessels—modifies arterial tone, exerting a vasodilatory effect [8, 22] and countering the vasoconstrictive action of compounds like angiotensin II [23], catecholamines [24] and endothelin [25].

Our results confirm the prohypertensive effect of ibuprofen [26], and suggest that ibuprofen acts more by extrarenal than renal inhibition of cyclo-oxygenase [27, 28, 29], since the reduction of urinary metabolites of thromboxane and prostacyclin observed after treatment with ibuprofen was more marked than for TXB₂ and 6-keto-PGF_{1 α} .

Consistent with this interpretation, we observed no effect on plasma and urinary creatinine, PRA, plasma renin release being partly prostaglandin-dependent [30], or urinary aldosterone. Alteration of these parameters would have been expected had water and sodium retention occurred. The prohypertensive effect of ibuprofen could thus depend on the prevalence of vasoconstrictive prohypertensive factors throughout the organism. Our results seem consistent with this hypothesis; however, ibuprofen treatment was not followed by increased vascular resistances in the musculo-cutaneous site explored. A clear definition of the effect of cyclo-oxygenase inhibition on regional vascular tone, as evaluated in the present study, would require more subjects, bearing in mind the high inter-subject variability in vascular resistances. Moreover, the findings of the present study do not give grounds for speculation on the effects of more prolonged administration of cyclo-oxygenase inhibitors in hypertensive patients treated with amlodipine.

Since we observed no increase in urinary prostacyclin metabolites after 1 month's treatment with amlodipine, we do not consider that antagonism of the antihypertensive activity of amlodipine after cyclo-oxygenase blockade necessarily implies amlodipine-

induced prostacyclin synthesis. A more reasonable hypothesis is that prostacyclin acts on blood pressure and reduces peripheral resistance, irrespective of possible treatment with calcium antagonists.

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