all the related specialties such as immunology, bacteriology, radiology, pathology, and cardiac anaesthesia, in association with skilled medical and nursing care.

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Attenuation of hypotensive effect of propranolol and thiazide diuretics by indomethacin

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Summary and conclusions

The effects of 100 mg indomethacin daily for three weeks on blood pressure and urinary excretion of prostaglandin $F_{2\alpha}$ were studied in a double-blind, placebo-controlled comparison of two groups of patients with essential hypertension, eight receiving propranolol and seven thiazide diuretics. Compared with placebo, adding indomethacin to the patients' established antihypertensive treatment increased blood pressure by 14/5 mm Hg supine and 16/9 mm Hg erect in the patients receiving propranolol, and by 13/9 mm Hg supine and 16/9 mm Hg erect in the patients receiving thiazide diuretics (all $p \leq 0.05$). The excretion of the major urinary metabolite of prostaglandin $F_{2\alpha}$ was reduced by 67% in the propranolol-treated patients and by 57% in those receiving a thiazide diuretic. Body weight increased by 0·8 kg (propranolol) and 1·1 kg (thiazide diuretic) when indomethacin was given, but there were no significant changes in creatinine clearance, urinary sodium excretion, or packed cell volume in either treatment group.

These results suggest that products formed by the arachidonic acid cyclo-oxygenase contribute to the regulation of blood pressure during treatment with both propranolol and thiazide diuretics. Inhibition of the cyclo-oxygenase with indomethacin partially antagonises the hypotensive effect of these drugs.

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Introduction

Beta-receptor-blocking drugs lower systemic blood pressure, but the mechanism is not established. Negative cardiac chronotropic[1] and inotropic[2] effects, anti-renin effects,[3] and central nervous system effects[4] may all contribute to their hypotensive action in man. Initially, systemic vascular resistance is raised after beta-receptor blockade.[5] During chronic beta-receptor blockade, however, systemic vascular resistance often falls towards pre-treatment values, despite the persistently reduced cardiac output.[6 7] Whether this is due to a change in the sensitivity of the baroreflex arc,[8] down-regulation of adrenergic receptors,[9] reduced concentrations of angiotensin II, or some other mechanism is uncertain. Durão *et al*[10] proposed that chronic beta-receptor blockade may stimulate formation of vasodilator prostaglandins, since indomethacin, a potent inhibitor of prostaglandin synthesis,[11 12] can attenuate the hypotensive effect of chronic propranolol treatment in man.[10] We therefore undertook a study to examine the specificity of this effect. In two groups of patients with essential hypertension, one receiving propranolol, the other a thiazide diuretic, we compared the effects of adding 100 mg indomethacin daily or placebo over three weeks in a randomised, cross-over study. A major urinary metabolite of prostaglandin $F_{2\alpha}$, prostaglandin $F_{2\alpha}M$, was measured as an index of the inhibition of total prostaglandin synthesis.

Patients and methods

We selected for the study 15 patients with mild essential hypertension. Supine blood pressure was controlled at 150/95 mm Hg or below with single-drug treatment. Eight patients (five men, three women) were being treated with 60-320 (mean 168) mg propranolol daily and seven (five men, two women) with a diuretic (five were receiving 5-10 mg bendrofluazide and two one to two tablets of Moduretic (amiloride 5 mg and hydrochlorothiazide 50 mg per tablet) daily). The propranolol-treated group were aged 50 ± 4 years and the diuretic-treated group 57 ± 3 years. The patients were otherwise healthy and, in particular, free from dyspeptic symptoms. Blood urea

and electrolyte concentrations, biochemical profile, blood count, and results of urine analysis were all normal. The protocol was approved by the research ethics committee of this hospital, and all patients gave written consent to the study.

In double-blind, randomised, cross-over fashion all patients received 50 mg indomethacin capsules or matching placebo twice daily for three weeks in addition to their usual antihypertensive drugs. Sodium intake was not restricted. To minimise gastrointestinal side effects subjects were instructed to take the indomethacin after meals and given a supply of 375 mg aluminium hydroxide tablets to take as necessary. The study comprised a two-week run-in period; two treatment periods, each lasting three weeks, separated by a two-week washout; and a final assessment two weeks after the end of the second treatment period.

Blood pressure, heart rate, and body weight were measured under basal conditions in a clinical laboratory. Blood pressure was measured in triplicate using an automatic ultrasound recorder (Arteriosonde, Roche 1217). Heart rate was counted from the radial pulse over 60 seconds and measurements made after 10 minutes' lying and three minutes' standing. After three weeks of each treatment a 24-hour urine sample was collected in a polypropylene container for estimation of creatinine and sodium concentrations. Aliquots (50 ml) were stored at −20°C for later analysis of prostaglandin $F_{2\alpha}M$. 5α,7α-Dihydroxy-11-ketotetranor-prostan-1-16-dioic acid, the major urinary metabolite of prostaglandin $F_{2\alpha}$, was measured by a combined gas chromatography and mass spectrometry assay.[13] Venous blood was drawn for blood count and measurement of creatinine, urea, electrolyte, and plasma indomethacin concentrations. Indomethacin concentrations were measured by high-pressure liquid chromatography.[14] Compliance was determined both by weekly pill counts and by plasma indomethacin concentrations.

We compared data from the second and third weeks of indomethacin treatment with similarly derived data from the placebo phase. Statistical significance was determined by Wilcoxon's rank sum and signed rank tests.

Results

In the patients treated with propranolol (table I) body weight rose from 76·3 ± SEM 4·5 kg when they were receiving placebo to 77·1 ± 4·7 kg when they were receiving indomethacin ($p < 0·05$). Two weeks after they stopped taking indomethacin body weight was not significantly different from basal values. Supine blood pressure rose from 128/84 ± 3/3 mm Hg with placebo to 142/89 ± 4/3 mm Hg ($p < 0·05$, systolic and diastolic) with indomethacin. Similarly, erect blood pressure rose from 130/94 ± 5/3 mm Hg to 146/103 ± 6/3 mm Hg (systolic $p < 0·05$, diastolic $p < 0·01$—fig 1). Blood pressure had returned to basal values within two weeks after stopping indomethacin. Neither erect nor supine heart rate was influenced by indomethacin. Twenty-four-hour urinary excretion of prostaglandin $F_{2\alpha}M$ fell 67% from 48·7 ± 13·8 μg with placebo to 16·4 ± 5·1 μg with indomethacin ($p < 0·01$).

In the patients treated with thiazide diuretic (table II) body weight rose from 71·9 ± 2·7 kg with placebo to 73·0 ± 2·6 kg with indomethacin ($p < 0·05$) but had fallen to basal values two weeks after the patients stopped taking indomethacin. Supine blood pressure rose from 140/92 ± 6/4 mm Hg with placebo to 153/101 ± 7/3 mm Hg with indomethacin ($p < 0·05$, systolic and diastolic). Similarly, erect blood pressure rose from 140/100 ± 4/2 mm Hg to 156/109 ± 6/3 mm Hg (systolic $p < 0·05$, diastolic $p < 0·01$—fig 1). Blood pressure had returned to basal values two weeks after the patients stopped taking indomethacin. Supine and erect heart rates were not significantly changed by indomethacin. Twenty-four-hour urinary excretion of prostaglandin $F_{2\alpha}M$ fell by 57%, from 22·0 ± 4·2 μg with placebo to 9·4 ± 3·2 μg with indomethacin ($p < 0·01$). (One patient (case 11) suffered a haematemesis from an acute gastric erosion on the 16th day of indomethacin treatment, so only data from the second week of his indomethacin treatment period were included.)

Neither group of patients showed any significant differences in creatinine clearance, urinary sodium excretion, plasma urea and electrolyte concentrations, or packed cell volume after receiving indomethacin. Compliance was 92% overall as assessed by weekly pill counts. Indomethacin was detected in the plasma of all patients on the last day of indomethacin treatment. The plasma concentration was 1·20 ± 0·34 μmol/l (42·9 ± 12·2 μg/100 ml) in the propranolol-treated group and 0·90 ± 0·10 μmol/l (32·2 ± 3·6 μg/100 ml) in the diuretic-treated patients (NS). Urinary prostaglandin $F_{2\alpha}M$ concentrations did not correlate significantly with blood pressure, heart rate, body weight, or dose of antihypertensive drug at any time in either group of patients.

Because our study did not include a double-placebo period we compared urinary excretion of prostaglandin $F_{2\alpha}M$ in our patients with that in a group of patients matched for age, sex, and blood

TABLE I—*Results of treatment with indomethacin or placebo in hypertensive patients receiving propranolol*

Case No	Dosage of propranolol (mg)	Age (years)	Blood pressure (mm Hg)				Heart rate (beats/min)				Body weight (kg)		24-hour urinary prostaglandin $F_{2\alpha}M$ (μg)	
			Supine		Erect		Supine		Erect					
			Placebo	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin
1	80	28	124/75	134/75	111/87	129/93	52	54	73	69	68·4	68·9	38·4	15·9
2	160	55	120/80	139/88	144/112	155/114	71	64	65	70	82·3	82·6	12·4	3·3
3	160	59	127/87	152/90	122/83	152/98	61	65	71	66	59·5	59·5	50·2	27·4
4	60	44	123/75	135/87	123/87	144/101	62	61	61	58	61·4	62·0	76·6	43·0
5	240	56	114/86	134/95	127/94	140/113	61	61	64	63	85·5	86·6	31·3	2·1
6	160	45	133/82	130/81	125/91	123/93	58	64	68	71	86·5	88·0	130·2	12·7
7	160	62	141/90	164/97	156/101	177/110	70	65	68	66	73·1	73·5	39·1	24·0
8	320	47	139/96	151/102	132/96	145/100	56	62	62	67	93·6	96·0	11·0	2·9
Mean	168	50	128/84	142/89	130/94	146/103	61	62	67	66	76·3	77·1	48·7	16·4
SEM	29	4	3/3	4/3	5/3	6/3	2	1	2	1	4·5	4·7	13·8	5·1
Significance			Systolic $p < 0·05$ Diastolic $p < 0·05$		Systolic $p < 0·05$ Diastolic $p < 0·01$		NS		NS		$p < 0·05$		$p < 0·01$	

TABLE II—*Results of treatment with indomethacin or placebo in hypertensive patients receiving thiazide diuretics*

Case No	Diuretic	Age (years)	Blood pressure (mm Hg)				Heart rate (beats/min)				Body weight (kg)		24-hour urinary prostaglandin $F_{2\alpha}M$ (μg)	
			Supine		Erect		Supine		Erect					
			Placebo	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin
9	Moduretic (1 tablet)	42	117/84	114/86	127/96	128/97	68	66	81	84	80·2	80·8	23·4	10·7
10	Moduretic (2 tablets)	53	163/101	168/101	151/102	174/105	84	82	96	91	59·5	60·3	–	–
11	Bendrofluazide 10 mg	54	125/85	166/111	131/90	158/113	69	84	82	92	68·0	69·8	14·7	3·2
12	Bendrofluazide 10 mg	57	130/94	155/102	157/106	175/123	67	66	77	70	69·7	70·8	42·4	22·8
13	Bendrofluazide 5 mg	51	157/108	159/102	140/108	150/114	76	70	86	80	71·8	74·9	17·1	11·6
14	Bendrofluazide 5 mg	67	146/90	158/106	137/101	158/111	58	60	64	65	78·8	79·2	17·5	8·2
15	Bendrofluazide 5 mg	73	144/82	149/96	140/96	149/102	89	76	99	88	75·5	75·5	16·9	0
Mean		57	140/92	153/101	140/100	156/109	73	72	84	81	71·9	73·0	22·0	9·4
SEM		3	6/4	7/3	4/2	6/3	4	3	5	4	2·7	2·6	4·2	3·2
Significance			Systolic $p < 0·05$ Diastolic $p < 0·05$		Systolic $p < 0·05$ Diastolic $p < 0·05$		NS		NS		$p < 0·05$		$p < 0·01$	

pressure who received placebo and bendrofluazide for 10 weeks during a concurrent double-blind study (fig 2). Statistical comparisons were not performed because the patients were in different studies, but the results show that excretion of prostaglandin $F_{2\alpha}M$ was virtually identical in the two groups receiving bendrofluazide, was slightly increased by bendrofluazide treatment, and was considerably greater in patients receiving propranolol than in a similar group of untreated patients.

Discussion

Indomethacin 100 mg daily for three weeks attenuated the hypotensive action of both propranolol and thiazide diuretics. Mean supine blood pressure rose 14/5 mm Hg in the propranolol-treated group and 13/9 mm Hg in the thiazide-treated group after indomethacin. A double-placebo period was not included in this study, but the rises in blood pressure after indomethacin were compatible with almost complete inhibition of the antihypertensive effect of both propranolol and thiazides.[15]

Indomethacin inhibits arachidonic acid cyclo-oxygenase,[16] an essential step in the biosynthesis of all prostanoids including the E and F series, prostacyclin, and thromboxane A_2. We recently found a positive correlation between 24-hour urinary excretion of prostaglandin $F_{2\alpha}M$ and plasma concentrations of 6-oxo-prostaglandin $F_{1\alpha}$, the chemical hydrolysis product of prostacyclin (unpublished results). Thus the 57-67% inhibition of excretion of prostaglandin $F_{2\alpha}M$ produced by indomethacin in this study was probably accompanied by a similar degree of inhibition of vascular production of prostacyclin.

Reversal of the hypotensive effect of thiazide diuretics and propranolol by indomethacin suggests that the hypotensive mechanism of both these compounds may be partly due to increased production of a vasodilator prostanoid such as prostacyclin. A recent study showing increased plasma concentrations of 6-oxo-prostaglandin $F_{1\alpha}$ after both acute and chronic treatment with bendrofluazide[17] supports this hypothesis and is consistent with the reduced systemic vascular resistance associated with chronic treatment with thiazides.

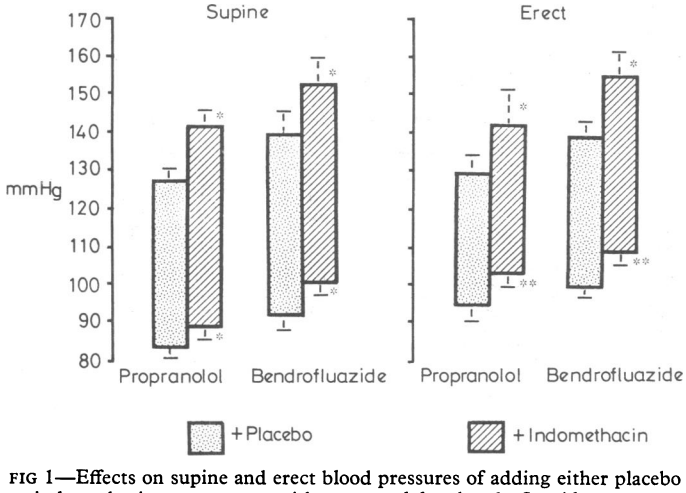

FIG 1—Effects on supine and erect blood pressures of adding either placebo or indomethacin to treatment with propranolol or bendrofluazide.
*p<0·05. **p<0·01.

An alternative explanation for our results may lie in the mild sodium retention that accompanies the use of indomethacin.[18] Sodium retention was probably responsible for the weight gain of about 1 kg in both groups. (A single estimation of 24-hour urinary sodium excretion showed no significant reduction after indomethacin in this study, but salt intake was not controlled.) Changes in salt and water balance might antagonise the hypotensive action of thiazides,[19] but the antagonism of the antihypertensive effects of propranolol is less easily explained. Sodium retention may itself depend on inhibition of prostaglandin synthesis in the kidney.[20]

These two hypotheses are not mutually exclusive, and the antagonism of the hypotensive effects of propranolol and thiazides may depend on different mechanisms. Furthermore, we

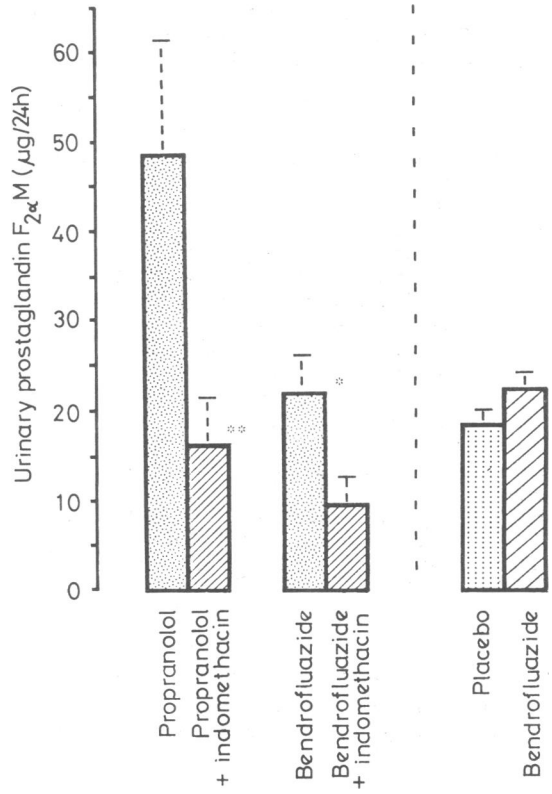

FIG 2—Twenty-four-hour urinary excretion of prostaglandin $F_{2\alpha}M$ before and after addition of indomethacin in patients receiving either propranolol or bendrofluazide. Shown for comparison are values in a matched group of hypertensive patients before and after 10 weeks' treatment with bendrofluazide.
*p<0·05. **p<0·01.

recently showed that salt loading in normal volunteers lowers the circulating concentration of 6-oxo-prostaglandin $F_{1\alpha}$ (unpublished results): thus sodium retention may cause reduced biosynthesis of prostacyclin and a rise in peripheral vascular resistance.

Another, less likely, possibility is that indomethacin itself may have had a pressor effect in these hypertensive subjects. Intravenous indomethacin causes a short-lived rise in systemic vascular resistance,[21] but the effects of long-term treatment with oral indomethacin on blood pressure in untreated patients with hypertension are conflicting.[22-25]

Our findings are of both theoretical and practical importance. On the theoretical level, inhibition of prostacyclin biosynthesis by indomethacin provides a possible explanation for the attenuation of the hypotensive effects of thiazide diuretics and beta-receptor-blocking drugs. On the practical level, our results show a drug interaction that is not widely appreciated and should be more frequently considered as a possible cause for poor blood-pressure control.

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Chronic stable asthma and the normal arterial pressure of carbon dioxide in hypoxia

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Summary and conclusions

Arterial blood-gas tensions, pH, and peak expiratory flow rate were measured in 29 patients with chronic asthma in a stable state. The hypoxia in these patients was found to be comparable with the hypoxia seen in normal subjects at high altitude in its effects on arterial pressure of carbon dioxide ($Paco_2$).

These results suggest that in patients with asthma the $Paco_2$ taken as normal should be related to the arterial oxygen tension. Any increase in the observed value compared with this predicted value indicates impaired respiratory control. This may well help in assessing the patients at greatest risk during an attack of asthma.

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Introduction

Patients with asthma often have an arterial carbon dioxide tension ($Paco_2$) lower than the generally accepted normal value. The same patients, however, may be moderately or even severely hypoxic. We consider that a parallel should be drawn with normal subjects acclimatised to the hypoxia of altitude, in whom $Paco_2$ is reduced linearly with hypoxia.[1] Patients with asthma may remain in a comparatively stable state with few symptoms and yet be hypoxic. If such patients respond to hypoxia in a similar fashion to normal subjects acclimatised to the hypoxia of high altitude they will also lower their $Paco_2$. In order to investigate this possibility we measured arterial oxygen tensions (Pao_2) and $Paco_2$ in patients with chronic stable asthma.

Patients and methods

Patients were prospectively selected for this study if they fulfilled five criteria. (1) They had a history of asthma since childhood; (2) peak expiratory flow rate or forced expiratory volume in one second increased by over 15% either spontaneously or after inhalation of 200 μg isoprenaline sulphate; (3) skin-prick tests to two common allergens were positive and there was a history suggesting that symptoms increased on exposure to these allergens; (4) there was an excess of eosinophils in the sputum or blood, or both; and (5) no appreciable change in exercise tolerance, wheeze, or tightness of the chest had occurred in the preceding week.