Effects of non-steroidal anti-inflammatory drugs on prostacyclin and thromboxane biosynthesis in patients with mild essential hypertension

P. MINUZ*, S. E. BARROW†, J. R. COCKCROFT & J. M. RITTER†

Department of Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN

1 The effects of non-steroidal anti-inflammatory drugs (NSAID) on prostacyclin and thromboxane biosynthesis and on blood pressure were determined in 46 patients with mild essential hypertension. Patients who had abstained from antihypertensive therapy for 2 weeks before study were treated with either aspirin, ibuprofen, sulindac or placebo for 7 days.

2 Excretion rates of 2,3-dinor-6-oxo-prostaglandin (PG) $F_{1\alpha}$, 6-oxo-PGF $_{1\alpha}$, 2,3-dinor-thromboxane (TX) B_2 and TXB $_2$ were measured as indices of prostacyclin and TXA $_2$ biosynthesis. Samples were assayed using immunoaffinity chromatography and gas chromatography/electron capture chemical ionisation mass spectrometry.

3 Aspirin and ibuprofen reduced urinary excretion of all prostacyclin- and thromboxane-derived products. Sulindac inhibited excretion of 2,3-dinor-6-oxo-PGF $_{1\alpha}$, 6-oxo-PGF $_{1\alpha}$ and 2,3-dinor-TXB $_2$, but had no significant effect on TXB $_2$.

4 Systolic blood pressure increased in the ibuprofen-treated group when compared with the placebo group. There were no other significant changes in systolic or diastolic pressure in any of the treatment groups. Among the patients as a whole, there was a significant negative correlation between change in blood pressure and change in excretion of the prostacyclin-derived but not of the thromboxane-derived products.

5 We conclude that, in patients with mild essential hypertension, neither sulindac nor aspirin (in the doses used) selectively spares prostacyclin biosynthesis by the kidney. The significant relationship between increase in blood pressure and reduction in prostacyclin biosynthesis favours the possibility that in individuals who become hypertensive, prostacyclin biosynthesis determines, in part, the severity of the hypertensive state.

Keywords prostacyclin thromboxane blood pressure hypertension NSAID

Introduction

Abnormal prostacyclin (PGI $_2$) and/or thromboxane (TX) A $_2$ biosynthesis in both the kidney and in the vasculature has been implicated in the pathogenesis of essential hypertension (Dunn &

Gröne, 1985; Hornyk *et al.*, 1983; Minuz *et al.*, 1990; Stoff, 1986; Wong *et al.*, 1986). These eicosanoids have opposing effects on vascular smooth muscle and on platelet aggregation and

Present addresses: *Clinica Medica, University of Verona, 37134, Verona, Italy.

† Department of Clinical Pharmacology, UMDS, Guy's Hospital, London Bridge, London SE1 9RT.

Correspondence: Dr S. E. Barrow, Department of Clinical Pharmacology, UMDS, Guy's Campus, London Bridge, London SE1 9RT

as such may contribute to both the increased vascular tone and the predisposition to thrombosis that characterise this condition. However, the precise role of abnormal PGI_2 and TXA_2 biosynthesis in essential hypertension is unknown. Non-steroidal anti-inflammatory drugs (NSAID) inhibit cyclo-oxygenase, the enzyme that catalyses the conversion of arachidonic acid to prostaglandin endoperoxides (Smith & Willis, 1971; Vane, 1971) which are the precursors of both PGI_2 and TXA_2 (Hamberg *et al.*, 1975; Moncada *et al.*, 1976). NSAID have been used to study the part played by eicosanoids in the control of blood pressure (Dunn & Gröne, 1985; Stoff, 1986).

Chronic administration of indomethacin or other NSAID has little effect on blood pressure in untreated hypertensive patients (Lopez-Ovejero *et al.*, 1978; Ylitalo *et al.*, 1978). However, several studies have shown that blood pressure generally increases when NSAID are given to patients treated with various anti-hypertensive drugs (Dunn & Gröne, 1985). Exceptions are aspirin and sulindac which do not increase blood pressure in these patients (Mills *et al.*, 1982; Puddey *et al.*, 1985; Steiness & Waldorf, 1982; Wong *et al.*, 1986). Several studies report that aspirin (Bucchi *et al.*, 1986) and sulindac (Patrono & Dunn, 1987) do not inhibit vasodilator prostaglandins in the kidney, which may account for their lack of effect on blood pressure. However, measurement of eicosanoid biosynthesis is difficult and not all studies have agreed that sulindac spares renal prostaglandin biosynthesis, possibly because of methodological limitations (Patrono & Dunn, 1987).

The purpose of this study was to compare the effects of ibuprofen (a non selective NSAID), sulindac and aspirin on the biosynthesis of renal and extra-renal PGI_2 and TXA_2 in patients with mild essential hypertension, and to determine whether inhibition of these eicosanoids is associated with changes in blood pressure. A non-invasive assessment of PGI_2 and TXA_2 biosynthesis *in vivo* was made by measuring hydration products and metabolites in urine. 6-Oxo- $\text{PGF}_{1\alpha}$ and TXB_2 are thought to be derived primarily from PGI_2 and TXA_2 biosynthesis in the kidney, whereas the 2,3-dinor-6-oxo- $\text{PGF}_{1\alpha}$ and 2,3-dinor- TXB_2 metabolites reflect extrarenal systemic biosynthesis (Catella *et al.*, 1986). We employed analytical methods based on gas chromatography/mass spectrometry to provide unequivocal measurements of these eicosanoids (Barrow & Taylor, 1987).

Methods

Subjects

Forty six patients (24 male and 22 female aged 31–54 and 35–67 years respectively) with mild essential hypertension gave written informed consent to participate in the study. Each patient had been diagnosed as hypertensive on the basis of five or more readings of diastolic blood pressure ≥ 90 mm Hg over a period of 6 weeks or longer. None had diastolic pressures ≥ 118 mm Hg, or systolic pressures ≥ 200 mm Hg. Seven patients (five men, two women) regularly smoked ≥ 10 cigarettes per day, while the remainder were non-smokers. At the time of recruitment, all but one was receiving anti-hypertensive therapy. There was no evidence of secondary hypertension on the basis of history, physical examination, urinalysis and urinary vanillyl mandelic acid excretion (< 35 mmol 24 h^{-1} on one or more occasion). Serum creatinine concentrations were all within the normal range of our laboratory ($70\text{--}125 \mu\text{mol l}^{-1}$).

Protocol

The protocol was approved by the Ethics Committee of Hammersmith and Queen Charlotte's Hospitals. Anti-hypertensive therapy was withdrawn from all patients for 2 weeks before study. No aspirin or other non steroidal anti-inflammatory drugs were taken for 2 weeks or more before study.

On the first study day, subjects collected urine from 08.00 h–08.00 h for eicosanoid, creatinine and electrolyte determinations. Patients were weighed and blood pressure was measured in triplicate using an automated indirect instrument (Dinamap; Critikon, Berkshire) between 10.00 h and 11.00 h on the day of urine collection after 60 min rest supine in a quiet room. A venous blood sample (15 ml) was taken for determination of creatinine and electrolytes, and for preparation of serum for TXB_2 determination by the method of Patrono *et al.* (1980). Patients were then randomly allocated to treatment for 7 days with either aspirin (300 mg 12 hourly; p.o.), ibuprofen (400 mg 8 hourly; p.o.), sulindac (200 mg 12 hourly; p.o.), or placebo (one tablet 12 hourly; p.o.) according to a double-blind balanced block design. Dose regimens were selected according to previously published data on effective inhibition of prostaglandin biosynthesis (Ciabattini *et al.*, 1984, 1987; Ritter *et al.*, 1989). On the 7th day, urine and blood were collected, and weight and blood pressure determinations were made as before.

Analysis

Prostaglandins and thromboxanes were assayed in urine using immunoaffinity chromatography and capillary column gas chromatography/electron capture mass spectrometry as described elsewhere (Barrow *et al.*, 1989). Briefly, urine samples (10 ml) were diluted 1:1 by volume with buffer at pH 8.0 and [$^2\text{H}_4$] 2,3-dinor-6-oxo-PGF $_{1\alpha}$, [$^2\text{H}_4$] 6-oxo-PGF $_{1\alpha}$, [$^2\text{H}_4$] 2,3-dinor-TXB $_2$, and [$^2\text{H}_4$] TXB $_2$ (5 ng each) were added. Samples were stored at -20°C . Prostaglandins and thromboxanes were extracted using CN-bromide activated sepharose columns containing immobilised antibodies which had been raised against 6-oxo-PGF $_{1\alpha}$ and TXB $_2$ and which cross-reacted with 2,3-dinor-6-oxo-PGF $_{1\alpha}$ and 2,3-dinor-TXB $_2$. Urine samples were applied under vacuum to the columns, which were washed with water (10 ml). Eicosanoids were eluted by addition of acetone:water (95:5 by volume; 1 ml) and rotating the columns for 15 min. Samples were taken to dryness (N_2 stream) and were derivatised as 3,4-bis-trifluoromethylbenzyl esters, trimethylsilyl ethers (Barrow & Taylor, 1987). They were stored in *n*-dodecane (15 ml) with desiccant. Aliquots (2.5 ml) were analysed using a Finnigan 4500 GC/mass spectrometer (Finnigan, San Jose, California) using the electron capture mode with ammonia as reagent gas. Carboxylate anions at m/z 585 were monitored for 6-oxo-PGF $_{1\alpha}$ and TXB $_2$ and at m/z 589 for their deuterated internal standards. Ions at m/z 557 and 561 were monitored simultaneously for the 2,3-dinor metabolites and their deuterated internal standards respectively. The detection limit for each eicosanoid was 5 pg ml^{-1} when 10 ml urine samples were assayed.

Platelet TXB $_2$ production was measured by allowing blood (5 ml) to clot in a plain glass tube at 37°C for 1 h (Patrono *et al.*, 1980). Serum TXB $_2$ concentrations were then measured using a previously validated radioimmunoassay (Burch *et al.*, 1979). Urine pH was recorded. Plasma and urinary creatinine, Na^+ and Ca^{+2}

were measured using routine methods in the Chemical Pathology Laboratory at Hammersmith Hospital.

Statistical analysis

Results are expressed as mean $\pm$ s.e. mean. Differences between eicosanoid production within the four treatment groups were analysed using a paired two-tailed Student's *t*-test and were considered significant when $P < 0.05$. A comparison of blood pressure between the four treatment groups was made using an analysis of variance with 95% confidence intervals. Correlations were sought using the method of least squares linear regression, and considered significant when $P < 0.05$.

Results

Excretion rates of eicosanoids before, and following 7 days treatment with NSAID or placebo are shown in Figure 1. Urinary excretion rates of the eicosanoids were not significantly different after treatment with placebo. Urinary excretion of 2,3-dinor-TXB $_2$, 2,3-dinor-6-oxo-PGF $_{1\alpha}$ and 6-oxo-PGF $_{1\alpha}$ were significantly reduced by all three NSAID. TXB $_2$ excretion was significantly reduced by aspirin and ibuprofen but not by sulindac.

Mean serum TXB $_2$ concentrations before and during treatment with NSAID or placebo are shown in Figure 2. There was no significant change in serum TXB $_2$ concentrations in the placebo-treated group. Each NSAID significantly inhibited serum TXB $_2$ production. The effect of aspirin was significantly greater than that of ibuprofen or sulindac.

Mean systolic and diastolic blood pressures before and after treatment with placebo, aspirin, sulindac or ibuprofen, are shown in Table 1. There was a significant increase in the systolic blood pressure of patients receiving ibuprofen when compared with the placebo group. There

Table 1 Mean ($\pm$ s.e. mean) systolic and diastolic blood pressures in patients with mild essential hypertension before, and following 7 days treatment with either placebo, aspirin, ibuprofen or sulindac

	Placebo (<i>n</i> = 12)	Aspirin (<i>n</i> = 12)	Ibuprofen (<i>n</i> = 10)	Sulindac (<i>n</i> = 12)
Systolic before (mm Hg)	150 (4)	148 (3)	150 (5)	155 (4)
Diastolic before (mm Hg)	93 (3)	92 (3)	95 (3)	93 (3)
Systolic after (mm Hg)	146 (3)	150 (4)	156 (5)	156 (5)
Diastolic after (mm Hg)	92 (2)	93 (3)	97 (2)	95 (2)

Figure 1 Mean ($\pm$ s.e. mean) excretion rates of 2,3-dinor-6-oxo-PGF_{1α}, 6-oxo-PGF_{1α}, 2,3-dinor-TXB₂, and TXB₂ in patients with mild essential hypertension following 2 weeks without antihypertensive therapy and following 7 days treatment with either placebo, aspirin, ibuprofen or sulindac (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

Figure 2 Mean ($\pm$ s.e. mean) serum TXB₂ concentrations in patients with mild essential hypertension following 2 weeks without antihypertensive therapy or NSAID, and following 7 days treatment with either placebo, aspirin, ibuprofen or sulindac.

were no other significant changes in systolic or in diastolic blood pressure between any of the treatment groups. Among the patients as a whole, there was a significant negative correlation between the change in excretion of 2,3-dinor-6-oxo-PGF_{1α} and changes in systolic ($r =$

0.475; $P < 0.001$) and diastolic ($r = 0.316$; $P < 0.05$) blood pressure (Figure 3). The slopes of the regression lines were such that a decrease of 2,3-dinor-6-oxo-PGF_{1α} excretion of 100 ng g⁻¹ creatinine was associated with a rise in systolic pressure of 9 mm Hg and a rise in diastolic pressure of 5 mm Hg. Similarly, there was a significant negative correlation between the change in 6-oxo-PGF_{1α} excretion and both systolic ($r = 0.257$; $P < 0.05$) and diastolic ($r = 0.312$; $P < 0.05$) blood pressure (Figure 4). A reduction of 100 ng g⁻¹ creatinine 6-oxo-PGF_{1α} was associated with increases of 8 mm Hg systolic and 7 mm Hg diastolic blood pressure. In contrast, there were no significant correlations ($P \geq 0.1$) between blood pressure and excretion of either 2,3-dinor-TXB₂ (Figure 5) or TXB₂ (Figure 6).

There were no significant correlations between eicosanoid excretion rates and urine pH, sodium or calcium excretion either before, or during treatment with NSAID. There was no significant change in body weight in any group.

Figure 3 Correlation between changes in excretion of 2,3-dinor-6-oxo-PGF_{1α} and blood pressure (BP) in 46 patients with mild essential hypertension following 7 days treatment with either placebo (●), aspirin (○), ibuprofen (□) or sulindac (Δ) (systolic: $r = 0.475$; $P < 0.001$; diastolic: $r = 0.316$; $P < 0.05$).

Figure 4 Correlation between changes in excretion of 6-oxo-PGF_{1α} and blood pressure (BP) in 46 patients with mild essential hypertension following 7 days treatment with either placebo (●), aspirin (○), ibuprofen (□) or sulindac (Δ) (systolic: $r = 0.257$; $P < 0.05$; diastolic: $r = 0.312$; $P < 0.05$).

Discussion

Simultaneous measurements of excretion rates of 6-oxo-PGF_{1α}, TXB₂ and their dinor metabolites in response to NSAID have not been reported previously in patients with essential hypertension. The present findings agree with earlier studies in healthy subjects which show that aspirin inhibits 2,3-dinor-6-oxo-PGF_{1α} and 2,3-dinor-TXB₂ which represent systemic extra-renal PGI₂ and TXA₂ biosynthesis (Fitzgerald *et al.*, 1983; Ritter *et al.*, 1989).

There was no significant difference between the inhibition of 6-oxo-PGF_{1α} excretion by ibuprofen, aspirin or sulindac, showing that in subjects with mild hypertension, neither aspirin nor sulindac spares renal PGI₂ biosynthesis. Inhibition of 6-oxo-PGF_{1α} and 2,3-dinor-6-oxo-PGF_{1α} excretion was similar with all three drugs indicating that renal and extra-renal PGI₂ biosynthesis are inhibited to a similar extent. Our results contrast with the report by Bucchi *et al.*

(1986) who found that one acute dose of oral aspirin (1 g) had no effect on excretion of 6-oxo-PGF_{1α} in healthy subjects. Ciabattini *et al.* (1980, 1984) found that the same dose of sulindac as used in the present study did not inhibit urinary 6-oxo-PGF_{1α} excretion in healthy subjects, or in patients with chronic glomerular disease. However, a number of comparative studies have failed to confirm the selectivity of sulindac (Brater *et al.* 1985; Roberts *et al.*, 1985; Wong *et al.*, 1986). The reason for the different findings is unclear, but it seems unlikely that they reflect the disease processes. Conflicting evidence regarding selectivity of sulindac has been attributed to limitations in analytical methodology (Patrono & Dunn, 1987). In particular, some studies have employed radio-immunoassay techniques which do not take account of antibody cross reactivity between 6-oxo-PGF_{1α} with its dinor metabolite. In this

Figure 5 Changes in excretion of 2,3-dinor-TXB₂ vs blood pressure (BP) in 46 patients with mild essential hypertension following 7 days treatment with either placebo (●), aspirin (○), ibuprofen (□) or sulindac (Δ) (systolic: $r = 0.176$; $P \geq 0.1$; diastolic: $r = 0.095$; $P \geq 0.1$).

study, we have used highly selective and specific techniques, which allow simultaneous quantification of both 6-oxo-PGF_{1 α} , 2,3-dinor-6-oxo-PGF_{1 α} as well as TXB₂ and 2,3-dinor-TXB₂ in a single urine sample.

Excretion of urinary TXB₂ was reduced following treatment with aspirin and ibuprofen. However, we found that sulindac had no significant effect on TXB₂ excretion confirming the work of Wong *et al.* (1986). The basis of the different effects of sulindac on renal PGI₂ and TXA₂ biosynthesis is unknown but may reflect different sites of production of these eicosanoids within the kidney. Sulindac is a pro-drug converted to an active sulphide metabolite which may be inactivated at certain sites within the kidney (Duggan *et al.*, 1977). This process may provide an explanation for the lack of inhibition of renal TXA₂ by sulindac.

Previous studies on the effects of NSAID in normotensive and in untreated hypertensive patients show little or no change in blood pressure (Dunn & Gröne, 1985; Lopez-Ovejero *et al.*, 1978; Mills *et al.*, 1982; Ylitalo *et al.*, 1978). We found an increase in blood pressure

Figure 6 Changes in excretion of TXB₂ vs changes in blood pressure (BP) in 46 patients with mild essential hypertension following 7 days treatment with either placebo (●), aspirin (○), ibuprofen (□) or sulindac (Δ) (systolic: $r = 0.045$; $P \geq 0.1$; diastolic: $r = 0.100$; $P \geq 0.1$).

only in the ibuprofen-treated group. However, the numbers of patients in each treatment group were small, and inhibition of cyclo-oxygenase by NSAID *in vivo* varies markedly between individuals. Taken together, these factors may mask an overall effect on blood pressure. A more appropriate approach is to assess the relationship between blood pressure and inhibition of eicosanoid biosynthesis and we found significant correlations between the degree of inhibition of PGI₂ biosynthesis and increases in blood pressure. The correlation coefficients suggest that differences in PGI₂ biosynthesis account for only a small part of the observed variation in blood pressure. We would not have expected to have observed effects of much greater magnitude than this in view of the many other factors independent of prostaglandin biosynthesis that influence blood pressure acutely, notably stress and anxiety. We attempted to reduce such variability by using carefully standardised conditions for blood pressure measurement in all patients. Changes in blood pressure were not correlated with inhibition of TXA₂ biosynthesis.

Assessment of the relationship between blood pressure and eicosanoid excretion within each treatment group would require larger numbers of subjects and is beyond the scope of the present study.

We have previously shown that there are significant negative correlations between blood pressure and PGI₂ but not TXA₂ biosynthesis in patients with essential hypertension (Minuz *et al.*, 1990), and argued that a selective impairment of PGI₂ production determines, in part, the severity of the hypertensive state. The present study supports this by showing that

changes in blood pressure during treatment with NSAID are also significantly correlated with inhibition of PGI₂ biosynthesis.

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