Effects of flurbiprofen on renal function in patients with moderate renal insufficiency

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- 1 Renal function was assessed in eight patients with chronic renal insufficiency following the administration of flurbiprofen 50 mg as a single dose and after chronic administration of 50 mg four times daily for 8 and 27 days. Diet and fluid intake were controlled.
- 2 Inulin and creatinine clearances and urinary excretion of sodium were measured at baseline and every 20 min for at least 3 h after dosing. The time of the mean peak concentration of (S)-flurbiprofen was used to guide the analysis of the clearances. Creatinine clearance, urinary excretion of sodium, and serum sodium and potassium were also assessed for 24 h after the dose and on a daily basis. Body weight and blood pressure were measured on a daily basis.
- 3 Decrements in inulin and creatinine clearances were small and reversible within 3 h of an oral dose of flurbiprofen. Comparison of baseline clearances for the three study periods (first dose and at 8 and 27 days of chronic dosing) revealed a lack of chronic effect on glomerular filtration rate.
- 4 In contrast, flurbiprofen caused a substantial (73 to 86%) and progressive decrease in the urinary excretion of sodium that reached a nadir within 4–5 h after drug administration. However, comparison of baseline values did not differ, indicating that balance conditions had been re-established.
- 5 Results of 24 h assessments were in agreement with the clearance study results. Reduced urinary excretion of sodium appeared to be limited to the first few days of flurbiprofen administration. Serum potassium concentration increased by $0.44 \text{ mEq l}^{-1} \pm 0.14$ within the first week after chronic flurbiprofen dosing, but then decreased to baseline despite continued administration of the drug. Body weight and systolic and diastolic blood pressures remained relatively stable while patients received flurbiprofen in conjunction with a controlled sodium diet but in the absence of the controlled diet they increased by $2.8 \pm 0.4 \text{ kg}$, $26.7 \pm 7.5 \text{ mm Hg}$, and $12.1 \pm 4.6 \text{ mm Hg}$, respectively.
- 6 Flurbiprofen administration at this dosage appears to cause no overall chronic adverse effects on renal function in patients with moderate renal insufficiency. Serum potassium concentration, patient weight and blood pressure increase to a minor degree but to an extent likely to be clinically important in some patients.

Keywords flurbiprofen adverse renal effects glomerular filtration natriuresis

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are known to affect renal function in susceptible patients by inhibiting the synthesis of vasodilating renal prostaglandins (Brater, 1988; Clive & Stoff, 1984). Among the risk factors for NSAID-associated reductions in

renal function are clinical conditions that render renal function prostaglandin-dependent such as cirrhosis (Zipser *et al.*, 1979), congestive heart failure (Cannon, 1986; Oliver *et al.*, 1981), and chronic renal insufficiency (Berg & Talseth, 1985; Brater *et al.*, 1985, 1987;

Ciabattoni *et al.*, 1984; Eriksson *et al.*, 1990; Swainson & Griffiths, 1985; Toto *et al.*, 1986; Whelton *et al.*, 1990). Upon administration of NSAIDs to patients with these disorders, glomerular filtration rate (GFR) decreases and independent of this effect, urinary excretion of sodium and potassium also decrease (Brater, 1988; Clive & Stoff, 1984). In patients with chronic renal insufficiency, numerous reports have documented these effects upon exposure to a variety of NSAIDs (Berg & Talseth, 1985; Brater *et al.*, 1985, 1987; Ciabattoni *et al.*, 1984; Eriksson *et al.*, 1990; Swainson & Griffiths, 1985; Toto *et al.*, 1986; Whelton *et al.*, 1990). However, studies have also documented that an acute adverse effect can be observed without a cumulative effect over time (Berg & Talseth, 1985; Brater *et al.*, 1985; Swainson & Griffiths, 1985; Toto *et al.*, 1986). Because the renal effects may vary among the available NSAIDs, newly marketed NSAIDs and those not previously studied must be studied individually. Flurbiprofen, an arylpropionic acid NSAID, was marketed in the United States in 1989 but has been available in other countries since the late 1970s (Brogden *et al.*, 1979). Its effects on renal function in patients with chronic renal insufficiency have not been ex-

amined systematically. We therefore studied the acute and chronic effects of flurbiprofen on renal function in patients with moderate chronic renal insufficiency.

Methods

Originally, this study was designed to assess the effects of oral flurbiprofen (Ansaid Tablets®, The Upjohn Company) on renal function in patients with renal insufficiency using indomethacin as a positive control. However, it became apparent after several patients were randomized to receive indomethacin that this NSAID had intolerable adverse effects in two of the three patients to whom it was administered. For ethical reasons and because indomethacin had previously been studied in patients with renal insufficiency, the protocol was modified to delete the indomethacin arm of the study. Eight patients, age 49 to 68 years, completed the flurbiprofen study arm but only one patient received the full course of indomethacin therapy. Two other patients had indomethacin stopped prematurely owing to adverse effects. Patient characteristics appear in Table 1.

Table 1 Characteristics of patients with chronic renal insufficiency

Patient number	Age (years)	Sex	Weight (kg)	Entry CL_{cr} * (ml min ⁻¹)	Diagnoses	Concomitant medications
<i>Flurbiprofen</i>						
1	49	M	87.2	44	Polycystic kidney disease, hypertension	Enalapril, frusemide, metoprolol
2	66	M	62.6	29	Hypertension	Clonidine, enalapril
3	59	M	85.6	40	Peripheral vascular disease, hypertension, coronary artery disease	Captopril, frusemide, isosorbide dinitrate, nifedipine, quinidine, nitroglycerine patch
4	59	M	55.3	27	Hypertension, emphysema	Albuterol inhaler, hydrochlorothiazide, reserpine, propoxyphene, theophylline
5	55	M	71.5	47	Hypertension, coronary artery disease, peripheral vascular disease	Clonidine, isosorbide dinitrate, nifedipine, nitroglycerine
6	68	F	73.5	29	Hypertension, coronary artery disease, gout	Enalapril, ferrous sulphate, frusemide, minoxidil, verapamil
7	51	M	68.0	20	Focal segmental glomerular nephritis, hypertension	Diltiazem, frusemide, prazosin, nifedipine
8	65	M	90.6	41	Diabetes mellitus	Enalapril, frusemide, insulin, nifedipine
<i>Indomethacin</i>						
9	54	M	57.0	43	Hypertension	Frusemide, propranolol
10	58	M	77.9	37	Diabetes mellitus, congestive heart failure, hypertension, peripheral vascular disease	Captopril, frusemide, insulin
11	59	M	69.6	41	Diabetes mellitus, coronary artery disease, chronic pancreatitis	Diltiazem, fludrocortisone, insulin, isosorbide dinitrate, nitroglycerine, pancreatic enzymes, ranitidine

* CL_{cr} = creatinine clearance

The eight patients who received flurbiprofen have been described previously (Knadler *et al.*, 1992).

Patients

Prior to enrollment a medical history was taken, and physical examination, electrocardiogram, vital signs, and endogenous creatinine clearance and other laboratory studies were obtained. Informed consent was obtained from each patient. The study was approved by the Indiana University Medical Center Institutional Review Board.

Inclusion criteria required that patients be 18–75 years of age with moderate renal insufficiency (creatinine clearance 20–60 ml min⁻¹). Patients were excluded if any of the following were present: known hypersensitivity or intolerance to any NSAID or aspirin; history of peptic ulcer disease, gastrointestinal bleeding or frequent dyspepsia; anaemia over and above that which would be expected from the patient's renal insufficiency; use of corticosteroids, NSAIDs, aspirin or aspirin-containing products unless the patient could refrain from taking these medications for 1 month prior to enrollment in the study and for the duration of the study. Also excluded were women of childbearing age who were not surgically sterile or not actively practicing contraception (IUD in place or taking oral contraceptive).

Patients remained on stable regimens of their chronic medications as shown in Table 1. Smokers and non-smokers were permitted to participate in the study. However, consumption of alcoholic beverages was not permitted during the study period. Patients were asked to avoid strenuous exercise immediately before and during the study.

Study design and clinical protocol

This was a randomized open-label, parallel study lasting 47 days with both inpatient and outpatient phases (Figure 1). Patients were admitted to the General Clinical Research Center (GCRC) for dietary equilibration throughout days 1 to 14. Sodium and potassium intake were 150 mEq and 60–80 mEq per day, respectively, and dietary fluids were 3 l per day. On day 6, patients were randomised to receive their first dose of either flurbiprofen or indomethacin 50 mg, and the first of

three renal clearance studies (*vide infra*) was performed. Patients were continued on either flurbiprofen 50 mg orally four times per day (with meals and bedtime snack) or indomethacin 50 mg orally three times per day with meals throughout days 7 to 13 and days 15 to 32. The second renal clearance study (day 14) was performed after patients had received their assigned study NSAID for 8 days. On day 15, patients had vital signs assessed and were then discharged from the GCRC but returned for evaluation as outpatients on days 19 and 26 to check for adverse symptoms and to assess serum electrolytes and creatinine concentration. On day 32, patients returned to the GCRC for the study diet and third renal clearance study on day 33 after having received chronic dosing of their assigned study NSAID for 27 days. Study NSAIDs were discontinued after this third renal clearance study following which patients returned to the GCRC on days 46 and 47 for a final measurement of creatinine clearance. Vital signs were also assessed on days 46 to 48.

Patients kept daily records of their medication recording all doses taken and all that were missed. Compliance was also checked with tablet counts which revealed that >90% of the doses of study NSAID were taken.

Clearance studies

Inulin and creatinine clearance and sodium excretion rate were assessed on days 6, 14, and 33 representing studies of the effects of NSAID following the first dose (study 1), and after 8 days (study 2) and 27 days (study 3) of continuous drug administration. Breakfast was withheld on these days. At the end of a 24 h urine collection that began the previous day, patients had an intravenous catheter inserted in each arm: one for the infusion of inulin and the other for blood sampling. A loading dose of inulin was administered as a 10% w/v solution at a dose of 50 mg kg⁻¹ of body weight followed by a continuous infusion at a rate of 0.25 mg times the estimated glomerular filtration rate in ml min⁻¹. Following the inulin loading dose a 45 min equilibration period began during which patients ingested a distilled water load of 20 ml kg⁻¹ to ensure adequate urine output. At the end of the equilibration period patients voided urine. Beginning with the equilibration sample, urinary output was matched with an equal volume of intravenous 5% w/v dextrose and water. After the equilibration period, three 20 min control urine collections with midpoint serum samples were obtained. After completion of the control collections, the patients were given a single 50 mg dose of either flurbiprofen or indomethacin by mouth. Following drug ingestion nine 20 min urine collections with midpoint serum samples were obtained. After completion of the 180 min collection period the inulin infusion and the intravenous fluid replacement were stopped. Patients were then allowed lunch. Urine samples were then collected hourly to 8 h and at 10, 12, and 24 h after dosing. Serum samples were also collected at 8, 10, 12 and 24 h. Blood and urine samples were analyzed for inulin, creatinine, potassium, sodium, and flurbiprofen and its metabolites. The pharmacokinetic data are reported separately (Knadler *et al.*, 1992).

Figure 1 Study calendar. Letters in the upper, left corner of each block represent either inpatient (i) or outpatient (o) days. Hatched blocks represent variable extended time periods.

Balance studies

During inpatient days and outpatient days 19 and 26, 24 h urine collections and serum samples were obtained and analyzed for sodium, potassium, and creatinine.

Analytical procedures

Serum and urine concentrations of inulin and creatinine were measured with an autoanalyzer (Technicon Instruments Corporation, Terrytown, NY, USA). The method for inulin in serum and urine was based upon the standard test for measuring carbohydrates using the anthrone method (Wright & Gann, 1966), whereas creatinine was measured using the Jaffe reaction. Individual standard curves were prepared for assay of each patient's samples. If the predicted concentration of external standards differed by more than 5% from their actual values, the assay was rerun.

Sodium and potassium were measured simultaneously with an IL943 Automatic Flame Photometer (Allied Instrumentation Laboratory, Lexington, MA, USA). Commercial standards were measured every 10 to 15 samples, and if their predicted value varied by more than 5% from the actual value, the samples were reanalyzed.

Data analysis

Clearance studies Previous studies of the effects of several NSAIDs in patients with chronic renal insufficiency have revealed that reductions in renal function, as reflected by glomerular filtration and sodium excretion rates following NSAID administration, are reversible. For clearance techniques, this transient effect results in a parabolic response-time curve. We therefore used the time of the peak concentration of (S)-flurbiprofen, the active enantiomer, to mark the beginning of the linear descent to the nadir of renal function, that is, the maximal drug effect. This method assumes no hysteresis between the serum concentration of the NSAID and its renal effect, an assumption that seems reasonable in view of other studies that have assessed concordance of concentrations with renal effects (Brater *et al.*, 1985, 1987; Toto *et al.*, 1986).

We first calculated the mean control value as the mean of two to three stable parameter values obtained prior to flurbiprofen administration for each patient. Stable values were those with a consistent urine volume. Using pharmacokinetic data from Knadler *et al.* (1992), we then determined the mean time of the maximum concentration of (S)-flurbiprofen (mean $t_{\max}$). Reasoning that the maximum renal effect of flurbiprofen would occur at or shortly after the mean $t_{\max}$, we compared the mean control with all experimental samples that occurred one 20 min collection period beyond the mean $t_{\max}$. For study 1, the mean $t_{\max} \pm$ s.e. mean after the first dose was 145 ± 43 min. Therefore, experimental samples up to 160 min were compared with the mean control. Similarly, the mean $t_{\max}$ for study 2 occurred at 113 ± 16 min so all experimental samples up to 140 min were submitted for analysis whereas the mean $t_{\max}$ for study 3 occurred at 136 ± 22

h so all experimental samples up to 160 min were analyzed.

We calculated the change from baseline by subtracting the value for each of the experimental measurements from the mean control. Fisher's least significant difference multiple comparison procedure was then used to determine the significance of the effects of flurbiprofen on renal clearance parameters (inulin and creatinine clearance, and sodium excretion rate) from baseline (Winer, 1971). We also assessed the reduction in renal function with time using repeated measures analysis of variance.

One-way analysis of variance was used to compare mean control measurements of inulin and creatinine clearance, and sodium excretion rate between studies 1, 2, and 3. Doing so, we assessed the chronic effects of flurbiprofen on these parameters in comparison to baseline renal function in the absence of flurbiprofen (study day 6), after 8 days (study day 14), and after 27 days (study day 33).

Balance studies Paired *t*-tests were used to assess the effects of flurbiprofen on daily serum sodium and potassium concentrations, total urinary sodium/24 h, and creatinine clearance. For these analyses, the mean control value was calculated as the mean of the values for days four and five (immediately prior to first flurbiprofen administration) by which time dietary equilibration had occurred. We calculated the change from baseline by subtracting the value for each of the measurements for days 7–13, 19, 26, and 32 from the mean control. We then tested the hypothesis that the change from baseline did not differ from zero.

Results are expressed as mean $\pm$ s.e. mean. Statistical analyses were considered significant if $P < 0.05$.

Results

Effects of indomethacin

Of the three patients randomized to receive indomethacin, only patient 10 completed the study. Two patients (9 and 11) were removed from the study prematurely owing to adverse effects from indomethacin. Patient 9 was removed on day 12 because of a 3 kg weight gain, peripheral oedema, and a rise in serum creatinine concentration from 1.6 to 1.9 mg%. Upon discontinuation of indomethacin, this patient's weight and serum creatinine concentration returned to baseline values, and the oedematous condition resolved. Patient 11 was removed from the study on day 15 because of a decrease in haemoglobin from 9.3 g dl^{-1} to 7.7 g dl^{-1} accompanied by haematest positive stools. This patient was asymptomatic and thought to have had an upper gastrointestinal bleed or gastritis. This problem resolved after indomethacin was discontinued.

Because of early discontinuation of indomethacin therapy owing to adverse effects in that study arm and subsequent discontinuation of that arm after only three patients had been enrolled, there were insufficient data to analyze for indomethacin effects. Thus, the remaining results focus upon flurbiprofen.

Effects of flurbiprofen

Clearance studies

Renal haemodynamics Clearance data for patients receiving flurbiprofen appear in Figures 2 and 3. Differences between the inulin clearance mean controls (time 0) and experimental collections were small and not statistically significant for studies 1 and 2 (Figure 2, a and b). In study 3, however, decrements in inulin clearance of 27.4% and 25.4% occurred at experimental collections of 60 and 100 min, respectively (Figure 2c). These reductions were transient and fully reversible by the mean $t_{\max}$ ($P > 0.05$). Comparison of the mean controls for inulin clearance among study 1, study 2, and study 3 revealed small increments that were not statistically significant indicating no cumulative effect of flurbiprofen on inulin clearance with repeated dosing ($F = 1.05$, $P = 0.37$).

A pattern similar to that for inulin clearance was observed for creatinine clearance (Figure 3 a to c). For study 1, significant but reversible decrements in creatinine clearance of 19.4% and 18.0% occurred at 60 and 80 min, respectively (Figure 3a). For study 2, decrements of 24.8% and 18.2% occurred at 80 and 100 min, respectively (Figure 3b). Again the decrements were transient. For study 3, decrements occurred earlier and were more prolonged (Figure 3c). Decrements from the mean control for this latter study ranged from 25.0% to 41.6% but had begun increasing by 180 min. It appears that control values in this study are inordinately high; therefore, the decrements detected may have little meaning. It is important to note that if the mean control for study 1 (prior to flurbiprofen use) had been used for comparison of the study 3 experimental collections, none of the decrements observed in study 3 would have reached statistical significance.

Figure 2 Mean ($\pm$ s.e. mean) inulin clearance values after the first flurbiprofen dose (study 1, panel a), and after 8 days (study 2, panel b) and 27 days (study 3, panel c) of continuous dosing. Time 0 is the mean control (see text). The vertical dashed line represents the mean time of the maximum serum concentration of S-flurbiprofen. * $P < 0.05$ compared with the control value for that study day.

Figure 3 Mean ($\pm$ s.e. mean) creatinine clearance values after the first flurbiprofen dose (study 1, panel a), and after 8 days (study 2, panel b) and 27 days (study 3, panel c) of continuous dosing. Format as in Figure 2.

Differences among the mean controls for studies 1, 2, and 3 were not significant ($F = 1.26$, $P = 0.30$) indicating no cumulative effect of flurbiprofen on creatinine clearance.

Renal sodium excretion In contrast to the acute, transient effects of flurbiprofen on renal haemodynamics, there was clearly a progressive effect of flurbiprofen on sodium reabsorption (Figure 4a to c). During studies 1, 2, and 3, a substantial number of collection periods showed a significant decrease in sodium excretion. For study 1, decrements reached statistical significance at 60 min and had not returned to baseline throughout the period of observation (Figure 4a). The nadir occurred at 4 h when excretion diminished to 75.0% of the mean control (data not shown in Figure 4). As such, these results indicate a time effect of flurbiprofen on sodium excretion up until the mean $t_{\max}$ ($F = 3.53$, $P = 0.004$). However, this time effect was not observed during study 2 owing to increased variability caused by one outlier (Figure 4b). For this study, patient 8 had an inordinately high sodium excretion (73% greater than the mean for the other patients), apparently due to dietary indiscretion. This resulted in a loss of the time effect ($F = 1.75$, $P = 0.13$). Removal of this patient from analysis resulted in a return of the time effect despite fewer degrees of freedom ($F = 3.58$, $P = 0.007$). As with study 1, the nadir occurred 4 h after administration of flurbiprofen. Similar effects were observed for study 3 (Figure 4c). In this study decrements reached a nadir 85.6% less than the mean control occurred at 5 h ($F = 3.10$, $P = 0.009$).

Comparison of the mean controls for urinary sodium excretion among studies 1, 2, and 3 revealed a significant increment between study 1 and study 3 ($F = 5.50$, $P < 0.02$). This higher urinary sodium excretion with chronic therapy may be the result of a compensatory mechanism preventing cumulative sodium retention with repeated flurbiprofen administration. More likely, however, it is due to the shorter dietary equilibration period (one day) in study 3 as compared with studies 1 and 2 (5 and 13 days, respectively). In

summary, these data are entirely consistent with the known reduction of renal tubular sodium reabsorption caused by NSAIDs.

Balance studies The results of the daily studies of creatinine clearance, urinary sodium excretion, and serum sodium and potassium appear in Figure 5a to d. Values for daily serum creatinine concentration (data not shown) were consistent with the findings from the clearance studies indicating no cumulative decrement in renal function throughout 28 days of flurbiprofen therapy (Figure 5a). Although daily excretion of sodium was significantly reduced on days 7, 9, and 11 throughout the period of dietary control, urinary excretion was moderately elevated on outpatient days 19, 26, and inpatient day 32 when no special diet was used (Figure 5b). There were no statistically significant changes in serum sodium concentration while patients received flurbiprofen (Figure 5c).

In contrast to the lack of effects of flurbiprofen on serum sodium concentration, serum potassium concentration was significantly elevated on study days 8, 10, and 12 (Figure 5d). Serum potassium concentration increased from a mean control value of 4.31 ± 0.20 to 4.75 ± 0.23 mEq l⁻¹ on day 12 ($+0.44 \pm 0.14$). Only one patient's increase in serum potassium concentration from the mean control exceeded 1.0 mEq l⁻¹ (Patient 12); this patient's mean control was the lowest (3.3 mEq l⁻¹). No patients' serum potassium concentration exceeded 6.0 mEq l⁻¹. In two patients serum potassium concentrations rose above 5.0 mEq l⁻¹ but returned to baseline values in both despite continued flurbiprofen administration.

Effect on weight and blood pressure Weight and blood pressure were increased, particularly in the absence of the controlled diet, which is consistent with the effects noted of sodium retention (Figure 6). As can be seen in Figure 6a, patient weights were slightly elevated from the mean control value ($73.5 \text{ kg} \pm 4.1$) throughout inpatient days 7 to 15. However, mean weight increased

Figure 4 Mean ($\pm$ s.e. mean) urinary excretion of sodium after the first flurbiprofen dose (study 1, panel a), and after 8 days (study 2, panel b) and 27 days (study 2, panel c) of continuous dosing. mEq min⁻¹ = mmol min⁻¹. Format as in Figure 2.

Figure 5 Mean ($\pm$ s.e. mean) effects of chronic flurbiprofen dosing on daily patient creatinine clearances (panel a), urinary excretion of sodium (panel b, $mEq/24\ h = mmol/24\ h$), serum sodium concentration (panel c, $mEq\ l^{-1} = mmol\ l^{-1}$), and serum potassium concentration (panel d, $mEq\ l^{-1} = mmol\ l^{-1}$). The mean control (MC) is the mean result of measurements made on days 4 and 5, immediately prior to the patient's first flurbiprofen dose.

further following patient discharge from the GCRC to a maximum value of $76.3 \pm 4.2\ kg$ ($+ 2.8 \pm 0.4\ kg$) on day 26, presumably reflecting an increase in dietary sodium intake in conjunction with flurbiprofen administration. Following the discontinuation of flurbiprofen administration on day 33, patient weights remained slightly but significantly higher than the mean control value (days 46 to 48.).

Similarly, systolic and diastolic blood pressures were elevated in the outpatient phase of the study (Figure 6b and c). Systolic blood pressure rose from a mean control value of $124.1 \pm 7.4\ mm\ Hg$ to a peak of $150.8 \pm 6.5\ mm\ Hg$ ($+ 26.7 \pm 7.5\ mm\ Hg$) on day 26 (panel B) whereas diastolic blood pressure rose from a mean control of $79.4 \pm 1.7\ mm\ Hg$ to a peak of $91.5 \pm 3.5\ mm\ Hg$ ($+ 12.1 \pm 1.7\ mm\ Hg$) on day 26 (Figure 6c). Systolic and diastolic blood pressure diminished after flurbiprofen was withdrawn (days 46 to 48).

Discussion

Chronic renal insufficiency may render renal haemodynamics and electrolyte homeostasis prostaglandin-dependent. Upon administration of NSAIDs to susceptible patients with pre-existing renal disease, synthesis of renal prostaglandins is reduced or abolished resulting in decrements in renal function and, independent of this haemodynamic effect, reduced excretion of sodium and potassium (Brater, 1988; Clive & Stoff, 1984). In such

patients, NSAIDs may cause acute ischaemic insult to the kidney that becomes clinically manifest by increases in serum creatinine and urea nitrogen. The effect on sodium reabsorption may cause weight gain, oedema, and increased blood pressure. Lastly, the hyporeninaemic-hypoaldosterone effect may cause hyperkalemia (Tan *et al.*, 1979).

The degree to which patients with renal insufficiency are susceptible to the effects of NSAIDs may depend upon sodium balance, the type and extent of renal disease, and the type of NSAID administered. Earlier studies assessed the renal effects of NSAIDs in sodium deplete patients with renal diseases thereby confounding the effect of the disease *per se* (Dunn & Zambraski, 1980). Recent studies have employed a controlled diet in which patients received fixed intakes of modest amounts of sodium (100 to $150\ mEq\ day^{-1}$) and potassium (60 to $80\ mEq\ day^{-1}$). In several such studies of patients with systemic lupus erythematosus (SLE) and other chronic glomerular diseases there was a linear correlation between glomerular filtration rate and prostacyclin synthesis (as determined using urinary excretion of 6-keto prostaglandin $F_{1\alpha}$) (Ciabattini *et al.*, 1984; Patrono *et al.*, 1985; Patrono & Pierucci, 1986). Renal function may also decline with NSAID administration to patients with renal diseases caused by hypertension or diabetes such as those in this study suggesting that prostaglandins are needed to maintain renal perfusion in this setting (Berg & Talseth, 1985; Brater *et al.*, 1985, 1987; Eriksson *et al.*, 1990; Toto *et al.*, 1986; Whelton *et al.*, 1990).

Figure 6 Mean ($\pm$ s.e. mean) effects of chronic flurbiprofen dosing (days 7 through 33) on daily patient weights (panel a), and systolic and diastolic blood pressures (panels b and c). The mean control (MC) was calculated as in Figure 5.

Flurbiprofen caused small and inconsistent decrements in inulin and creatinine clearance measurements that were reversible within 3 h of administration. Furthermore, comparison of the mean control clearance measurements for studies 1, 2, and 3 revealed a lack of cumulative decrements with up to 27 days of continuous flurbiprofen administration. These results are in agreement with those of similar studies in which the administration of other NSAIDs was 2 to 11 days (Berg & Talseth, 1985; Eriksson *et al.*, 1990; Toto *et al.*, 1986; Whelton *et al.*, 1990) and one study in which the GFR of six patients with chronic renal disease was unaffected following 27 days of continuous sulindac administration (Swainson & Griffiths, 1985). As such, the results provided added reassurance that chronic administration of flurbiprofen up to 28 days does not cause cumulative decrements in GFR in patients with moderate chronic renal insufficiency.

In contrast to the modest effect of flurbiprofen on

GFR, a substantial reduction in urinary excretion of sodium was observed that reached a nadir at 4–5 h after dosage administration. Renal prostaglandins are natriuretic, blocking sodium reabsorption in the nephron by interfering with chloride transport across the thick ascending limb of Henle and increasing renal medullary blood flow (Ickhikawa & Brenner, 1980; Kaojarern *et al.*, 1983; Kirchner, 1985; Kokko, 1981). Upon administration of NSAIDs, the natriuretic effect of prostaglandins is diminished. Sodium retention and/or reduced response to diuretics are a well described result. Although none of the patients who received flurbiprofen experienced increased oedema, net sodium accumulation and mild increases in weight and blood pressure occurred.

In summary, data from the clearance studies indicate a modest, reversible effect on renal haemodynamic parameters, but a consistent effect of flurbiprofen in causing decreased sodium excretion and its attendant clinical effects. Interestingly, there were different time-response profiles for the haemodynamic parameters compared with that observed for urinary excretion of sodium. This is presumably due to the existence of separate compartments for prostaglandin effects, as has been previously suggested by McGiff *et al.* (1979). The haemodynamic effect is probably due to vascular endothelial production of PGI_2 , which would be readily accessed by circulating NSAID. In contrast, the renal tubular effect on sodium reabsorption is probably due to PGE_2 , which may be more remote from circulating NSAID.

In terms of chronic effects of flurbiprofen (Figures 5 and 6), creatinine clearance was decreased by 18 to 24% on day 7 and 8 compared with control, indicating that with chronic therapy there may be a slight decrement in creatinine clearance. It is of interest that on subsequent days there was no decline in creatinine clearance compared with control, indicating a recovery of renal function with persistent dosing. Urinary sodium excretion was decreased on days 7, 9, and 11 compared with control values and this effect was consistent with that observed in the clearance studies, namely, a mild sodium retentive effect of the NSAID associated with the subsequent weight gain and blood pressure increase with increased dietary sodium (Figure 6). There were no significant changes in serum sodium concentration throughout the study. Lastly, serum potassium concentrations were found to be slightly but significantly higher on days 8, 10, and 12 compared with control values. This effect is undoubtedly due to the hyporeninaemic-hypoaldosterone syndrome known to occur with NSAIDs (Brater, 1988; Clive & Stoff, 1984). The magnitude of this elevation was not clinically relevant.

In conclusion, this study of the effects of flurbiprofen in eight patients with moderate renal insufficiency indicates transient effects on renal haemodynamics. There was also a reduction in urinary excretion of sodium with first and subsequent doses associated with weight gain and increase in blood pressure. An increase in serum potassium also occurred, which returned to baseline despite continued dosing. Thus, there appeared to be no overall chronic adverse effect of flurbiprofen on renal function in these patients. These findings are

consistent with the lack of accumulation of flurbiprofen in such patients (Knadler *et al.*, 1992). Additionally, the effects were qualitatively similar though somewhat less than those that we have observed in similar studies of such patients administered indomethacin and keto-

profen (Toto *et al.*, 1986) and etodolac (Brater *et al.*, 1985, 1987).

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