Effects of tenoxicam on renal function and the disposition of inulin and *p*-aminohippurate in healthy volunteers and patients with chronic renal failure

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- 1 The effects of tenoxicam on renal function were studied in 10 patients with chronic renal failure (creatinine clearance $46.7 \pm 11.9 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$) and eight healthy volunteers. A parallel treatment control group of eight healthy volunteers received placebo. Tenoxicam was given orally in a dose of 40 mg daily for 2 days followed by 20 mg daily for a further 8 days. Renal function was assessed by measurement of the renal clearances of inulin and *p*-aminohippurate (PAH) using the single injection technique before and during administration of tenoxicam.
- 2 In the healthy volunteers there were no changes in glomerular filtration rate, effective renal plasma flow, or the urinary excretion of *N*-acetylglucosaminidase and β_2 -microglobulin on the 3rd and 10th days of treatment with tenoxicam. The mean urinary excretion of prostaglandins E_2 and 6-keto $F_{1\alpha}$ decreased during treatment but there was great individual variation and the differences were not statistically significant. Tenoxicam had no effect on the half-life, clearance, volume of distribution or urinary recovery of inulin and PAH.
- 3 There was no significant change in the clearance of inulin and creatinine after treatment with tenoxicam for 10 days in the patients with chronic renal failure. However, in this group there was a significant increase in plasma creatinine on the 3rd and 6th days with a return to pretreatment levels by the 10th day. The administration of tenoxicam for 10 days was associated with a small but significant increase in the plasma half-life and volume of distribution of inulin. There was also a decrease in the clearance of PAH and an increase in its half-life.
- 4 In the patients with chronic renal failure tenoxicam produced a significant decrease in the urinary excretion of prostaglandin E_2 but not 6-keto prostaglandin $F_{1\alpha}$. There was no change in the excretion of *N*-acetylglucosaminidase or β_2 -microglobulin.
- 5 Tenoxicam had minor effects on renal function in the patients with chronic renal failure but as with other nonsteroidal anti-inflammatory agents it should be used with caution in patients who are predisposed to the adverse renal effects of these drugs.

Keywords inulin clearance PAH clearance non-steroidal anti-inflammatory drugs
tenoxicam prostaglandins *N*-acetylglucosaminidase β_2 -microglobulin
renal function nephrotoxicity chronic renal failure

Introduction

In recent years there has been much concern about the toxicity of non-steroidal anti-inflammatory drugs, including their adverse effects on the kidney. These drugs inhibit the synthesis of vasodilator renal prostaglandins and as a result they may cause acute (but usually re-

versible) reduction in renal function in individuals who are predisposed because of old age, underlying renal disease or conditions associated with decreased renal perfusion. Other prostaglandin-dependent adverse effects include hyperkalaemia and sodium and water

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retention with aggravation of cardiac failure and hypertension. In addition, the long term use of non-steroidal anti-inflammatory drugs may be complicated by papillary necrosis and chronic renal failure (analgesic nephropathy) (Carmichael & Shankel, 1985; Clive & Stoff, 1984; Prescott, 1982).

Tenoxicam is a recently introduced oxicam derivative and appears to share the general properties of the non-steroidal anti-inflammatory drugs which are related to inhibition of prostaglandin synthesis. It has a long duration of action with a plasma half-life of about 72 h (Gonzalez & Todd, 1987). The early clinical investigation of new non-steroidal anti-inflammatory drugs should include assessment of their actions on the kidney under different conditions, and in this report we describe the effects of tenoxicam on renal function in healthy volunteers and patients with chronic renal failure.

Methods

Healthy volunteers

This part of the study was randomized, double-blind and placebo controlled with parallel treatment of two groups of eight healthy male volunteers with oral tenoxicam or placebo. Comprehensive renal function studies were carried out before, and on the 3rd and 10th days of treatment. All the volunteers were healthy as judged by medical history, physical examination and routine biochemical and haematological screening. None drank excessively or took any drugs regularly. The mean ages and body weights of the tenoxicam and placebo groups were 27.9 ± 6.0 and 27.5 ± 2.6 years, and 69.5 ± 5.9 and 70.0 ± 8.6 kg, respectively. The subjects were asked to avoid alcohol and excessive salt intake during the study and to refrain from sexual activity for 36 h before the renal function study days to facilitate measurement of urinary prostaglandin excretion.

The control renal function studies were carried out during the week prior to treatment with tenoxicam or placebo. The volunteers attended at approximately 08.30 h and after the bladder was emptied they were weighed and blood was taken for biochemical analysis. A fluid load of 500 ml water was drunk over 5 min and hydration was subsequently maintained by the intake of 100 ml water every 30 min for the next 6 to 8 h. One hour after the initial water load, inulin (70 mg kg^{-1}) and *p*-aminohippurate (PAH, 10 mg kg^{-1}) were administered intravenously for estimation of the glomerular filtration rate and effective renal plasma flow by the single injection technique (McAuslane *et al.*, 1987; Prescott *et al.*, 1991). Divided urine collections were made and the urinary excretion of prostaglandins E_2 and 6-keto $F_{1\alpha}$, *N*-acetylglucosaminidase and β_2 -microglobulin was determined. The creatinine clearance was also measured over 8 h. These studies were repeated on the 3rd and 10th day of treatment with tenoxicam or placebo.

Patients with chronic renal failure

An open study of the renal effects of tenoxicam was performed in 10 outpatients (eight male) with stable

chronic renal failure due to hypertension (five patients), glomerulonephritis (two), chronic pyelonephritis (one), polycystic kidneys (one) and renal artery stenosis (one). Their mean age and body weight were 60.5 ± 7.0 years and 75.3 ± 7.8 kg, and the initial mean creatinine clearance was $46.7 \pm 11.9 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. None of the patients was taking ACE inhibitors, other non-steroidal anti-inflammatory drugs or histamine H_2 -receptor antagonists. Their regular drug therapy included β -adrenoceptor blocking drugs (seven patients), diuretics (five), nifedipine (three) and allopurinol (one), and these were continued as normal during the study.

The patients attended for 8 h on four occasions as follows: (1) at screening for admission to the study during the week before administration of tenoxicam, (2) on the day before the start of treatment with tenoxicam, (3) on the 10th and last day of treatment and (4) at follow-up 11 days after the last dose of tenoxicam. Detailed renal function studies including measurement of the inulin and PAH clearances by the single injection method were carried out as described above on the day before treatment (the control study) and on the 10th day of treatment with tenoxicam. The body weight, pulse rate, blood pressure and 8 h creatinine clearance were measured at each visit.

Drug administration

The active treatment group of healthy volunteers and the patients with renal failure received oral tenoxicam 40 mg (two tablets) with water at approximately 09.00 h on the first and second days followed by 20 mg daily for the next 8 days. The control group of healthy volunteers received matching placebo. All the subjects remained supine for the duration of the renal function studies. Compliance was assessed by measurement of plasma tenoxicam concentrations on the 3rd, 8th and 10th days of treatment in the healthy volunteers and on the 3rd, 6th and 10th days in the patients with renal failure.

Safety monitoring

In the healthy volunteers, urinalysis and routine haematological and biochemical screening (including measurement of the plasma urea, creatinine and electrolytes) were performed immediately before treatment and again on the morning of the last day of administration of tenoxicam. Similar comprehensive monitoring was carried out in the patients with chronic renal failure at the initial screening visit, on the last day of treatment with tenoxicam and at follow-up 11 days after the drug had been discontinued. The plasma creatinine was also monitored on the 3rd and 6th days of treatment with tenoxicam.

Informed consent was obtained from all the volunteers and patients, and the studies were approved by the local Ethics of Medical Research Committee.

Analytical methods

Standard laboratory methods were used for haematological and biochemical screening, and plasma and urine creatinine were estimated by the Jaffe reaction

(Gemstar ElectroNucleonics). Prostaglandins E₂ and 6-keto F_{1α} were determined by radioimmunoassay (Powell, 1980) as was β₂-microglobulin (Pharmacia). Urine N-acetylglucosaminidase was measured by spectrophotofluorimetry (Leaback & Walker, 1961). Inulin was determined by an automated colorimetric method (Dawborn, 1965), and PAH and acetyl-PAH were estimated by high performance liquid chromatography (McAuslane *et al.*, 1987). The intra- and interassay coefficients of variation for the measurement of plasma and urine PAH were less than 4% for the concentrations encountered in this study. Plasma tenoxicam was measured by the method of Dixon *et al.* (1984).

Pharmacokinetic analysis and calculation of glomerular filtration rate and renal plasma flow

The glomerular filtration rate and effective renal plasma flow were assumed to be equal to the renal clearances of inulin and PAH respectively. The plasma concentration-time data for PAH and inulin were fitted by open 1 and 2 compartment models respectively using the SIPHAR pharmacokinetic and curve fitting programme (Centres d'Etudes et de Recherches en Statistiques et Informatique Médicales, Creteil, Cedex-France.) The reciprocal of the square of the observations ($1/y^2$) was used as the weighting factor and in the case of inulin, the model was based on constant infusion of the dose over 5 min (Prescott *et al.*, 1991). The total clearance was calculated as the dose divided by the area under the plasma concentration-time curve (AUC) calculated from the model and extrapolated to infinity, and the renal clearance as the amount recovered in the urine divided by the corresponding AUC. The clearances of PAH and inulin were calculated using the plasma concentration and urinary excretion data obtained from 0 to 1 and 0 to 2 h in the healthy volunteers and from 0 to 2 and 0 to 3 h respectively in the patients with chronic renal failure. The kinetic analysis also provided estimates of the half life and steady state volume of distribution (V_{ss} : total clearance $\times$ mean residence time).

Statistical methods

The results are expressed as means $\pm$ standard deviation and the statistical significance of differences between

means was determined by analysis of variance taking $P < 0.05$ as the level of significance.

Results

Glomerular filtration rate

The mean pretreatment renal clearances of inulin were 109.9 ± 11.4 , 103.5 ± 10.2 and 39.1 ± 15.6 ml min⁻¹ 1.73 m⁻² respectively in the healthy volunteers receiving tenoxicam and placebo, and the patients with chronic renal failure. Tenoxicam had no significant effect on the glomerular filtration rate in any group at any time during treatment as judged by the renal and total clearances of inulin. Similarly, tenoxicam did not produce any significant change in the creatinine clearance (Table 1).

Although tenoxicam did not reduce the clearances of inulin and creatinine as measured above, it appeared to cause a temporary fall in the glomerular filtration rate in the patients with chronic renal failure. In these patients the plasma creatinine increased significantly from 190 ± 59 and 193 ± 65 μmol l⁻¹ before tenoxicam to 207 ± 71 and 212 ± 66 on the 3rd and 6th days of treatment, subsequently decreasing to 195 ± 65 on the last treatment day and 188 ± 62 μmol l⁻¹ 10 days after the drug was discontinued ($P < 0.01$) (Figure 1). This apparent reduction in glomerular filtration rate would not have been reflected in the clearance measurements because of their timing.

Figure 1 Plasma creatinine concentrations (Δ) and creatinine clearances (▨) before, during and after administration of tenoxicam for 10 days in 10 patients with chronic renal failure.

Table 1 Renal and total clearances of inulin and creatinine clearance before and during treatment with tenoxicam in patients with chronic renal failure, and with tenoxicam and placebo in healthy volunteers

	Treatment	Renal clearance of inulin			Total clearance of inulin			Creatinine clearance		
		Before	Day 3	Day 10	Before	Day 3	Day 10	Before	Day 3	Day 10
Healthy volunteers	Tenoxicam	109.9 ± 11.4	105.1 ± 12.7	103.7 ± 15.4	111.3 ± 13.6	105.8 ± 15.6	117.2 ± 21.3	111.3 15.3	110.6 17.5	109.7 13.2
Healthy volunteers	Placebo	103.5 ± 10.2	101.5 ± 16.2	103.6 ± 22.1	113.9 ± 11.7	108.2 ± 9.8	110.7 ± 22.5	105.5 6.3	108.8 11.8	111.1 18.8
Chronic renal failure patients	Tenoxicam	39.1 ± 15.6	–	39.5 ± 14.4	41.4 ± 14.8	–	39.6 ± 13.1	48.8 15.3	–	44.5 12.1

Clearances are given in ml min⁻¹ 1.73 m⁻² as means $\pm$ s.d.

Table 2 Renal and total clearances of *p*-aminohippurate (PAH) before and during treatment with tenoxicam in patients with chronic renal failure, and with tenoxicam and placebo in healthy volunteers

	Treatment	Renal clearance of PAH			Total clearance of PAH		
		Before	Day 3	Day 10	Before	Day 3	Day 10
Healthy volunteers	Tenoxicam	650 ± 110	696 ± 179	644 ± 114	740 ± 81	755 ± 174	745 ± 117
Healthy volunteers	Placebo	663 ± 119	705 ± 163	653 ± 97	780 ± 101	834 ± 169	785 ± 92
Chronic renal failure patients	Tenoxicam	158 ± 53	–	152 ± 60	260 ± 62	–	235* ± 64

Clearances are given as means ± s.d. in ml min⁻¹ 1.73 m²

* $P < 0.05$ compared with the control period before treatment with tenoxicam.

Inulin disposition

The mean values for the pretreatment plasma inulin half-life and volume of distribution in the combined group of 16 healthy volunteers were 73.5 ± 17.3 min and 0.183 ± 0.045 l kg⁻¹ respectively, and tenoxicam had no effect on the disposition of inulin in these subjects.

In the patients with chronic renal failure there was a small but significant increase in the plasma inulin half life from 179 ± 52 min before treatment to 200 ± 53 min after tenoxicam had been taken for 10 days ($P < 0.05$). This was associated with an increase in the volume of distribution of inulin from 0.128 ± 0.010 to 0.138 ± 0.013 l kg⁻¹ ($P < 0.05$).

Tenoxicam had no consistent effect on the urinary excretion of inulin and overall $79.0 \pm 9.2\%$ of the dose was recovered in 8 h in the patients with chronic renal failure and $96.8 \pm 8.8\%$ over the same period in the healthy volunteers.

Renal plasma flow

The mean pretreatment renal clearances of PAH in the healthy volunteers given tenoxicam and placebo and the renal failure patients were 650 ± 110 , 663 ± 119 and 158 ± 53 ml min⁻¹ 1.73 m⁻², respectively. As expected, the total clearance of PAH always exceeded the renal clearance (Table 2). Tenoxicam had no effect on the renal or total clearances of PAH in the healthy volunteers but there was a significant decrease in the total clearance of PAH from 260 ± 62 to 235 ± 64 ml min⁻¹ 1.73 m⁻² after treatment with tenoxicam in the patients with renal failure ($P < 0.05$) (Table 2).

PAH disposition

The mean initial plasma half-life and distribution volume of PAH in the two groups of healthy volunteers combined were 14.5 ± 1.5 min and 0.238 ± 0.030 l kg⁻¹, respectively. There were no differences between the groups or changes during treatment.

In the patients with chronic renal failure there was a minor but significant increase in the plasma half-life of PAH from 42.4 ± 7.3 min before treatment to 46.2 ± 9.4 min after tenoxicam for 10 days ($P < 0.05$). There was

no corresponding change in the volume of distribution (0.222 ± 0.024 compared with 0.216 ± 0.027 l kg⁻¹).

Tenoxicam had no effect on the urinary recovery of PAH and its acetylated metabolite. Overall, $77.1 \pm 5.1\%$ of the dose was recovered unchanged and $14.8 \pm 1.7\%$ was excreted as acetyl-PAH in 8 h in the combined groups of healthy volunteers. In the patients with chronic renal failure there was a slower elimination with more extensive metabolism and the corresponding recoveries of PAH and acetyl-PAH were 61.1 ± 7.4 and $23.0 \pm 3.7\%$, respectively.

Filtration fraction

The mean pretreatment filtration fraction was $16.6 \pm 2.9\%$ in the healthy volunteers and $24.6 \pm 4.0\%$ in the renal failure patients. There was no change in either group during administration of tenoxicam.

Urine prostaglandins, N-acetylglucosaminidase and β_2 -microglobulin

The urinary excretion of prostaglandin E₂ and 6-keto F_{1 α} was very variable and much greater in the healthy volunteers than the patients with chronic renal failure (Table 3). There was a fall in mean excretion rates in all groups during treatment but the decrease was statistically significant only with prostaglandin E₂ in the renal failure patients after exclusion of the data of one subject in whom the initial excretion rate was atypically high ($P < 0.01$).

The urinary excretion of β_2 -microglobulin was much greater and more variable in the patients with renal failure than in the healthy volunteers. There were no changes in the excretion of β_2 -microglobulin or N-acetylglucosaminidase in any of the groups during treatment with tenoxicam.

Fluid retention

Tenoxicam did not cause important fluid retention in any group. Thus during treatment there was no significant increase in body weight and blood pressure or evidence of haemodilution as shown by a reduction in plasma albumin or sodium concentrations.

Table 3 Urinary excretion of prostaglandins before and during treatment with tenoxicam in healthy volunteers and patients with chronic renal failure

	Treatment	Prostaglandin E ₂ (ng 24 h ⁻¹)			6-keto prostaglandin F _{1α} (ng 24 h ⁻¹)		
		Before	Day 3	Day 10	Before	Day 3	Day 10
Healthy volunteers	Tenoxicam	6229 ± 6135	2263 ± 1586	3579 ± 6774	1200 ± 507	811 ± 445	775 ± 296
Healthy volunteers	Placebo	5490 ± 7977	1251 ± 1633	3289 ± 5637	1281 ± 1102	737 ± 576	879 ± 674
Chronic renal failure patients**	Tenoxicam	209 ± 118	—	58* ± 39	99 ± 52	—	68 ± 16

* $P < 0.01$ compared with excretion rate before tenoxicam.

** 8 h collection only.

Plasma tenoxicam

Tenoxicam was present in the plasma of all subjects receiving active drug on every occasion. The mean concentrations were similar on days 8 and 10 in the healthy volunteers (6.6 ± 0.6 and 6.5 ± 0.7 mg l⁻¹) and on days 6 and 10 in the patients (7.0 ± 0.7 and 7.9 ± 0.9 mg l⁻¹ respectively).

Safety monitoring

Apart from the increases in plasma creatinine concentration in the patients with chronic renal failure mentioned above, there were no consistent changes in biochemical values which could be related to treatment with tenoxicam. There was a small but significant fall in haemoglobin on the 10th day in all groups which could have been related to blood sampling.

Discussion

The administration of tenoxicam for 10 days had no effect on the glomerular filtration rate or effective renal plasma flow in healthy volunteers, and there was no evidence of nephrotoxicity as shown by the urinary excretion of *N*-acetylglucosaminidase and β -microglobulin. These findings are much as expected since nonsteroidal anti-inflammatory drugs do not normally have adverse effects on renal function in healthy young subjects who are well hydrated and in normal sodium balance. Under these conditions renal blood flow and function are not dependent on the actions of vasodilator prostaglandins (Carmichael & Shankel, 1985; Clive & Stoff, 1984). The urinary excretion of prostaglandins E₂ and 6-keto F_{1α} (a stable metabolite of prostacyclin) was very variable in the healthy volunteers (presumably because of seminal contamination) and it was not possible to demonstrate significant inhibition of their output by tenoxicam. Previous studies of urinary prostaglandin excretion in men have pointed to similar difficulties in the interpretation of such data (Patrono *et al.*, 1979). There was much less variation in the patients with chronic renal failure and urinary prostaglandin excretion was much less than in the healthy volunteers.

Tenoxicam had variable minor effects on renal function in the patients with chronic renal failure. It did not reduce the glomerular filtration rate as shown by the inulin and creatinine clearances on the 10th day but there was a significant increase in plasma creatinine on the 3rd and 6th days of treatment. It is difficult to avoid the conclusion that tenoxicam produced a transient fall in glomerular filtration rate but there seemed to be rapid adaptation as the plasma creatinine had returned to previous levels by the 10th day despite continued administration of the drug. After treatment with tenoxicam there was also a small increase in the plasma half-life of inulin, and this appeared to be related more to an increased volume of distribution than to reduced clearance of inulin. The distribution volume could have expanded as a result of tenoxicam-induced fluid retention but we were unable to demonstrate such an effect. The urinary excretion of prostaglandin E₂ was reduced in the patients with chronic renal failure after treatment with tenoxicam, and there was a small decrease in the total (but not renal) clearance of PAH which was associated with minor prolongation of the plasma half-life.

These effects of tenoxicam were of little clinical significance but renal function was not severely impaired in our patients and they were in relatively normal fluid and sodium balance. It cannot be assumed that tenoxicam would not cause more serious adverse renal effects in other patients or the elderly under different conditions (Clive & Stoff, 1984; Gurwitz *et al.*, 1990). The renal effects of nonsteroidal anti-inflammatory drugs may depend critically on experimental conditions and in this context there were problems with the design of the present study. Flexibility was limited because tenoxicam has a very long half-life and treatment had to be continued for many days to approach steady state drug concentrations and response. In a previous report there was a significant (mean 13%) fall in the glomerular filtration rate measured by the clearance of Cr⁵¹ EDTA (but not a fall in renal blood flow or creatinine clearance) in 10 'high renal risk' patients following the administration of 20 mg tenoxicam daily for 5 days. It is not known whether this effect would have declined with continued treatment as in the present study. In addition, with one exception, there was no significant increase in plasma creatinine in 56 outpatients who took tenoxicam 20 mg daily for between 1 and 5 years (Giovannoni *et al.*,

1990). Treatment with tenoxicam does not seem to carry any greater risk than with other non-steroidal anti-inflammatory agents but it should be used with caution in the elderly and in patients who are predisposed to the adverse renal effects of these drugs, for example those

with sodium depletion, congestive cardiac failure and cirrhosis with ascites.

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