The comparative effects of paracetamol and indomethacin on renal function in healthy female volunteers

L. F. PRESCOTT, P. MATTISON, D. G. MENZIES & L. M. MANSON

University Department of Clinical Pharmacology, The Royal Infirmary, Edinburgh EH3 9YW

1 Renal function was assessed in 10 healthy female volunteers during administration of placebo, paracetamol (acetaminophen) (4.0 g daily) and indomethacin (150 mg daily) for 3 days under conditions of controlled sodium and fluid intake.

2 Paracetamol and indomethacin had no significant effect on the glomerular filtration rate and effective renal plasma flow as measured by the renal clearances of inulin, creatinine and *p*-aminohippurate (PAH).

3 Compared with placebo, paracetamol reduced the mean urinary excretion of prostaglandin E₂ by 43% on the second day and 58% on the third treatment day ($P < 0.01$). With indomethacin the corresponding reductions were 73 and 80%. Paracetamol and indomethacin had much less effect on the excretion of prostaglandin 6-keto F_{1α}, and a significant decrease was observed only on the third day.

4 The decreased urinary excretion of prostaglandin E₂, produced by paracetamol was associated with a reduction in sodium excretion of more than 50% ($P < 0.01$) and delay in the onset of diuresis following an acute water load.

5 The renal effects of paracetamol and indomethacin appear to differ. Although indomethacin reduced prostaglandin excretion more than paracetamol it had a similar effect on sodium excretion and less initial antidiuretic action. Unlike paracetamol, indomethacin also reduced basal plasma renin activity.

6 Paracetamol reduced the total body clearance of PAH and increased its plasma half-life. This effect could be attributed to inhibition of the acetylation of PAH by paracetamol.

7 In normal use paracetamol does not appear to have the adverse renal effects associated with the non-steroidal anti-inflammatory analgesics and further studies are required to establish the clinical significance of these findings.

Keywords paracetamol acetaminophen indomethacin adverse renal effects prostaglandins natriuresis water excretion glomerular filtration renal plasma flow inhibition of PAH acetylation

Introduction

The adverse effects of aspirin and the non-steroidal anti-inflammatory drugs on renal function have attracted considerable attention over the years. By inhibiting renal prostaglandin synthesis, these drugs interfere with water excretion and natriuresis, and under certain conditions they may reduce renal blood flow. The clinical consequences include weight gain,

oedema, hyponatraemia, hyperkalaemia and antagonism of the effects of diuretics and anti-hypertensive agents (Garella & Matarese, 1984; Oates, 1988). They may also cause acute impairment of renal function in patients who are predisposed by virtue of pre-existing renal disease, volume or sodium depletion, or reduced renal perfusion from any cause (Kimberly *et al.*, 1979).

In addition, non-steroidal anti-inflammatory analgesics can cause tubulo-interstitial damage, the nephrotic syndrome and renal papillary necrosis (analgesic nephropathy) (Blackshear *et al.*, 1985; Carmichael & Shankel, 1985; Levin, 1988).

Paracetamol (acetaminophen) does not seem to share those adverse effects of non-steroidal anti-inflammatory drugs which are attributed to general inhibition of prostaglandin synthesis. In particular, it is thought not to cause fluid and sodium retention or to impair renal function when taken in normal doses, and paracetamol alone has only been implicated rarely as a cause of analgesic nephropathy (Prescott, 1982). Because of the risks associated with the use of other analgesics, paracetamol is used extensively in patients with impaired renal function. Despite this wide use, very little is known of the acute effects of therapeutic doses of paracetamol on renal function. No information is available concerning its effects on renal prostaglandin synthesis in man but it has been reported to reduce sodium and water excretion (Haylor, 1980) and to have an antidiuretic effect in patients with diabetes insipidus (Nusynowitz & Forsham, 1966). In this report we describe the acute effects of paracetamol on renal prostaglandin synthesis, glomerular filtration rate, renal blood flow and renal function in healthy subjects under conditions of normal hydration and controlled sodium intake. The study was carried out in females to avoid problems with the estimation of urinary prostaglandins and a cross over design was used with placebo and indomethacin as controls.

Methods

Subjects

Ten healthy female volunteers took part in the study. Their mean age and body weight were 27 ± 6 years and 62.9 ± 10.9 kg respectively, and none smoked, drank alcohol or took any drugs regularly other than oral contraceptives. They were in good health as judged by medical history, physical examination, urinalysis and normal values on haematological and biochemical screening. Informed consent was obtained and the study was approved by the local ethics committee.

Study design and drug administration

Paracetamol (Panadol tablets 500 mg), indomethacin (Indocid capsules 25 mg) or placebo (lactose capsules) were given under single-blind

conditions for 3 consecutive days on three separate occasions at least 1 week apart with the order of treatments randomised according to a balanced block design. To avoid complications with pre menstrual fluid retention, studies were restricted to the 18 days following the end of a normal menstrual period. The shortest time for completion of the study in each individual was therefore 2 months. Comprehensive renal function studies were carried out on the second and third days of each of the three treatment periods. No observations were made on the first day.

On the first and second study days paracetamol (1.0 g) was taken at 08.30, 12.30, 16.30 and 20.30 h, and indomethacin (50 mg) and placebo at 08.30, 12.30 and 18.30 h. On the third day the drugs were taken at 08.30 and 12.30 h only.

For the assessment of renal function the volunteers fasted from 22.00 h in the previous night and a standard lunch without cooked meat was provided to minimise fluctuation in plasma creatinine concentrations. They were asked to keep to a diet which restricted sodium intake to 75 mmol day^{-1} for 2 days before and during the period of drug administration in order to reduce the variation in sodium excretion and to sensitise the kidney to the effects of renal prostaglandin depletion.

Renal function studies

On the second day of each treatment period, the glomerular filtration rate (renal clearances of inulin and creatinine), effective renal plasma flow (renal clearance of *p*-aminohippurate), plasma renin activity and the 8 h urinary excretion of sodium, potassium, prostaglandins E_2 and 6-keto $F_{1\alpha}$, *N*-acetylglucosaminidase and β_2 -microglobulin were measured.

The total body and renal clearances of inulin and *p*-aminohippurate (PAH) were estimated by the single intravenous injection technique (Freestone *et al.*, 1986; McAuslane *et al.*, 1987). The fasting volunteers took their drugs under supervision with 200 ml of water at 08.30 h and intravenous cannulae were inserted in both forearms. At 09.00 h 10 mg kg^{-1} of PAH and 70 mg kg^{-1} of inulin (Inutest, Laevosan Gesellschaft, Linz) were infused sequentially by pump over 1 and 5 min respectively. Blood was sampled from the opposite arm at 5, 10, 20, 30, 45, 60, 90, 120, 240, 360 and 480 min, and urine was collected from 0–1, 1–2, 2–4, 4–6, 6–8 and 8–24 h for estimation of PAH, inulin, creatinine, electrolytes, osmolality, *N*-acetylglucosaminidase, β_2 -microglobulin, and prostaglandins as appropriate. The plasma renin activity was measured

initially 30 min before and then 1 h after the administration of PAH and inulin under basal conditions. The volunteers remained recumbent for 8 h during the renal function studies and the total divided fluid intake over this period was 1 l. A light lunch was taken at 13.00 h.

At 09.00 h on the third day of each treatment period a fluid load of 15 ml kg⁻¹ of water was taken over 20 min under the same experimental conditions as on the previous day. Urine was collected from 0–2, 2–4 and 4–8 h for measurement of volume, pH, osmolality, and sodium, potassium, prostaglandins, *N*-acetylglucosaminidase and β_2 -microglobulin content. In one subject sodium excretion was very high on the third day of treatment with indomethacin and the data were omitted from the analysis. Plasma and urine samples were stored frozen.

Analytical methods

Inulin was estimated by an automated colorimetric method (Dawborn, 1965) and PAH by high performance liquid chromatography (McAuslane *et al.*, 1987). β_2 -Microglobulin (Pharmacia) and plasma renin activity (Haber *et al.*, 1969) were determined by radioimmunoassay, prostaglandins E₂ and 6-keto F_{1 α} according to Powell (1980) and creatinine, sodium, potassium and osmolality by standard laboratory methods. *N*-acetylglucosaminidase was estimated by spectrophotofluorimetry and the results are expressed as the ratio of μ mol of methylumbelliferone released in 30 min to mmol of creatinine in the sample.

Pharmacokinetic and statistical analysis

The plasma concentration-time data for inulin (0 to 2 h) and PAH (0 to 1 h) were fitted by an open two compartment model by weighted non-linear regression analysis using the SIPHAR pharmacokinetic curve fitting and modelling programme (Centres d'Etudes et de Recherches

en Statistiques et Informatique Médicales, Creteil, Cedex-France). This also provided estimates of model-independent variables. The total body clearance of inulin was calculated as the administered dose/the area under the plasma concentration-time curve (AUC) from 0 to 2 h extrapolated to infinity, and the renal clearance as the amount excreted in the urine in 2 h/AUC from 0 to 2 h. The total body and renal clearances of PAH were determined in the same way using the AUC from 0 to 1 h and the amount excreted in the urine from 0 to 1 h. The creatinine clearance was obtained as the amount excreted in 8 h divided by the corresponding AUC. The steady-state volumes of distribution (V_{ss}) of inulin and PAH were estimated as total body clearance $\times$ mean residence time.

Results are expressed as means $\pm$ s.d. and the statistical significance of differences between means was determined by two way analysis of variance and the Wilcoxon signed rank test. The level of significance was taken as $P < 0.05$.

Results

Glomerular filtration rate

Paracetamol and indomethacin had no statistically significant effect on the glomerular filtration rate as judged by the renal and total body clearances of inulin and the creatinine clearance (Table 1). The mean renal clearances of inulin during administration of placebo, paracetamol and indomethacin were 98 ± 19 , 93 ± 14 and 96 ± 22 ml min⁻¹ respectively.

Effective renal plasma flow

Similarly, the effective renal plasma flow as indicated by the renal clearance of PAH did not differ significantly between the treatment groups (Table 1). However, the mean total body clearance of PAH during treatment with

Table 1 Mean total body and renal clearances of inulin and *p*-aminohippurate, and creatinine clearance in 10 healthy female volunteers during administration of placebo, paracetamol and indomethacin (ml min⁻¹)

Treatment	Inulin		PAH		Creatinine clearance
	Total body clearance	Renal clearance	Total body clearance	Renal clearance	
Placebo	100 $\pm$ 18	98 $\pm$ 19	512 $\pm$ 105	422 $\pm$ 90	115 $\pm$ 14
Paracetamol	95 $\pm$ 15	93 $\pm$ 14	412 $\pm$ 109*	407 $\pm$ 69	114 $\pm$ 17
Indomethacin	93 $\pm$ 17	96 $\pm$ 22	538 $\pm$ 126	455 $\pm$ 122	109 $\pm$ 13

* $P < 0.05$ compared with placebo and indomethacin.

paracetamol was significantly less than with placebo and indomethacin (412 ± 109 compared with 512 ± 105 and $538 \pm 126 \text{ ml min}^{-1}$ respectively, $P < 0.05$) (Table 1). There were no significant changes in the filtration fraction.

Urinary excretion of prostaglandins E_2 and 6-keto $F_{1\alpha}$

The urinary excretion of prostaglandin E_2 was significantly reduced by paracetamol on both days (Table 2). Indomethacin had a greater effect and the reduction with both was more marked on the third than on the second day of treatment (Figure 1). Paracetamol reduced prostaglandin E_2 excretion by a mean of 43% on the second day and 58% on the third day while

the corresponding decreases with indomethacin were 73 and 80% respectively. Paracetamol and indomethacin had much less effect on the urinary excretion of prostaglandin 6-keto $F_{1\alpha}$. There was little change on Day 2 but with both drugs the decrease was statistically significant on Day 3 (Table 2).

No relationship could be demonstrated between the 0 to 8 h excretion of prostaglandin E_2 and sodium on either day. However, following the acute water load on Day 3, there were significant correlations between the 0 to 2 h excretion of prostaglandin E_2 and urine volume and sodium ($r = 0.49$ and 0.55 respectively, $P < 0.01$), and the 2 to 4 h excretion of prostaglandin E_2 and sodium ($r = 0.69$, $P < 0.001$). Similarly, the 0 to 2 h excretion of prostaglandin

Table 2 Mean 0–8 h urinary excretion of prostaglandin E_2 and 6-keto $F_{1\alpha}$ (ng) during administration of placebo, paracetamol and indomethacin in 10 healthy volunteers

Treatment	Day 2 Prostaglandin		Day 3 Prostaglandin	
	E_2	6-keto $F_{1\alpha}$	E_2	6-keto $F_{1\alpha}$
Placebo	225 ± 111	131 ± 28	183 ± 121	124 ± 32
Paracetamol	$129 \pm 102^*$	139 ± 86	$76 \pm 42^{**}$	$98 \pm 19^*$
Indomethacin	$61 \pm 55^{***}$	96 ± 43	$36 \pm 37^{***}$	$86 \pm 27^{**}$

* $P < 0.05$, ** $P = < 0.01$, *** $P = < 0.001$ compared with placebo.

Figure 1 Reduction in the 0 to 8 h urinary excretion of sodium (▨), prostaglandin E_2 (■) and prostaglandin 6-keto $F_{1\alpha}$ (□) during treatment with paracetamol and indomethacin in 10 healthy female volunteers. The results are expressed as the mean % decrease relative to administration of placebo.

Table 3 The urinary excretion of sodium and potassium during treatment with placebo, paracetamol and indomethacin in 10 healthy volunteers

Treatment	Day 2			Day 3	
	Sodium 0-8 h (mmol)	Sodium 0-24 h (mmol)	Potassium 0-8 h (mmol)	Sodium 0-8 h (mmol)	Potassium 0-8 h (mmol)
Placebo	39.2 ± 18.6	67.4 ± 28.8	31.1 ± 6.2	11.7 ± 6.7	27.5 ± 11.1
Paracetamol	18.7** ± 9.6	37.5* ± 18.9	27.2 ± 9.5	4.7** ± 4.6	31.6 ± 15.4
Indomethacin	23.3* ± 16.0	40.7* ± 33.1	31.8 ± 11.0	3.8** ± 2.8***	26.2 ± 10.8

* $P < 0.05$ compared with placebo, ** $P < 0.01$ compared with placebo, *** $n = 9$.

6-keto $F_{1\alpha}$ on Day 3 was correlated with the corresponding urine volume and sodium ($r = 0.66$, $P < 0.001$ and $r = 0.53$, $P < 0.01$), as was the 2 to 4 h excretion of prostaglandin 6-keto $F_{1\alpha}$ and sodium ($r = 0.37$, $P < 0.05$).

Sodium and potassium excretion

Paracetamol produced a striking and statistically highly significant reduction in sodium excretion which was at least as great as that observed with indomethacin (Table 3). With all three treatments, less sodium was excreted on the third than on the second day but the fractional decrease produced by paracetamol and indomethacin was similar on both occasions (Figure 1). During administration of paracetamol on Day 2 the sodium output was 18.7 ± 9.6 compared with 39.2 ± 18.6 mmol 8 h^{-1} with placebo, and the corresponding excretion rates on Day 3 were 4.7 ± 4.6 and 11.7 ± 6.7 mmol 8 h^{-1} respectively ($P < 0.01$). With the data from both days combined, paracetamol reduced the mean sodium excretion by 56% compared with 54% with indomethacin. Paracetamol and indomethacin had no significant effect on potassium excretion and as a result the urine sodium/potassium ratio was reduced correspondingly by both drugs.

Plasma renin activity

As expected, the plasma renin activity decreased significantly with all treatments after the volunteers had been recumbent for 1.5 h (Table 4, $P < 0.001$). Paracetamol had no effect on either the initial or subsequent basal plasma renin activity. However, at the latter time plasma renin activity was significantly lower during treatment with indomethacin than with paracetamol ($P < 0.05$).

Table 4 Plasma renin activity in 10 healthy volunteers during administration of placebo, paracetamol and indomethacin

	Placebo	Paracetamol	Indomethacin
Initial plasma renin activity (ng ml ⁻¹ h ⁻¹)	4.6 ± 2.8	5.0 ± 2.9	3.0 ± 2.6
Basal plasma renin activity (ng ml ⁻¹ h ⁻¹)	2.4 ± 1.3	2.7 ± 1.3	1.6 ± 1.6*

* $P < 0.05$ compared with paracetamol.

Urine volume and osmolality

Paracetamol delayed the onset of diuresis following the acute water load on the third treatment day, and the 0 to 2 h urine volume was significantly reduced compared with placebo (Table 5). Indomethacin had relatively little effect. During administration of paracetamol, only 34% of the fluid load was excreted in 2 h compared with 55 and 46% with placebo and indomethacin respectively. The 0 to 8 h urine volume on the second day was also lower with paracetamol (817 ± 213 ml) than with placebo (1026 ± 263) and indomethacin (1065 ± 363 ml) but the differences were not statistically significant. The mean body weights on the second day of treatment did not differ, and were 63.0 ± 11.6 , 63.3 ± 11.4 and 63.5 ± 12.8 kg with placebo, paracetamol and indomethacin respectively.

In parallel with the reduction in sodium excretion, there was a decrease in urine osmolality and osmolal clearance on the second day of treatment. The 0 to 8 h urine osmolalities during administration of placebo, paracetamol and indomethacin were 241 ± 59 , 196 ± 22 and 205 ± 34 respectively while the corresponding

Table 5 Urine output following ingestion of a water load of 15 ml kg⁻¹ in 10 healthy volunteers during administration of placebo, paracetamol and indomethacin

Time after water load	Placebo urine volume (ml) (% of load)	Paracetamol urine volume (ml) (% of load)	Indomethacin urine volume (ml) (% of load)
0–2 h	505 ± 227 (55)	309 ± 186* (34)	459 ± 297 (46)
0–4 h	760 ± 259 (81)	619 ± 214 (66)	734 ± 384 (75)
0–8 h	1247 ± 320	1328 ± 340	1314 ± 364

* $P < 0.05$ compared with placebo.

osmolal clearances were 1.77 ± 0.44 , 1.46 ± 0.17 and 1.51 ± 0.25 ml min⁻¹. In both cases the differences between placebo and paracetamol (but not indomethacin) were statistically significant ($P < 0.05$). There were no consistent changes in free water clearance. Urine osmolality was lower during diuresis on the third day and there were no significant differences between treatments.

Urinary excretion of N-acetylglucosaminidase and β_2 -microglobulin

The urinary excretion of β_2 -microglobulin and N-acetylglucosaminidase was not increased by paracetamol or indomethacin and thus there was no evidence of renal tubular toxicity. The combined N-acetylglucosaminidase to creatinine ratios on the second and third days of treatment with placebo, paracetamol and indomethacin were 13.3 ± 4.9 , 14.0 ± 3.7 and 14.3 ± 3.6 . The corresponding excretion rates of β_2 -microglobulin were 76 ± 49 , 59 ± 42 and 74 ± 33 $\mu\text{g h}^{-1}$.

Effects of paracetamol and indomethacin on the disposition of inulin and PAH

Pharmacokinetic variables relating to inulin and PAH are summarised in Table 6. There was a trend towards an increase in the plasma half-life, AUC, volume of distribution and mean residence time of inulin and PAH during treatment with paracetamol and indomethacin. The elimination half-life of PAH was prolonged with paracetamol (36.4 ± 14.1 min compared with 26.2 ± 6.5 min with placebo, $P < 0.05$) but otherwise the changes were not statistically significant. Except in the case of PAH with paracetamol, the plasma concentration-time curves of inulin and PAH were virtually superimposable during the three treatment periods (Figure 2).

Figure 2 Plasma concentrations of inulin (a) and PAH (b) following intravenous injection of 70 and 10 mg kg⁻¹ respectively in 10 female volunteers during administration of placebo (□), paracetamol (◇) and indomethacin (*).

The urinary recovery of PAH and inulin was similar with all treatments. During the first hour the urinary recoveries of total PAH with placebo, paracetamol and indomethacin were 76 ± 8 , 79 ± 16 and $75 \pm 14\%$ of the dose

Table 6 Effects of paracetamol and indomethacin on the disposition of inulin and *p*-aminohippurate (PAH) following rapid intravenous infusion in 10 healthy volunteers

Treatment	PAH					% Urinary recovery as acetyl-PAH in 8 h		Inulin	
	Plasma half-life (min)	V_{ss} (l)	Mean residence time (min)	$AUC(0, \infty)$ ($\text{mg l}^{-1} \text{h}$)	Mean residence time (min)	$AUC(0, \infty)$ ($\text{mg l}^{-1} \text{h}$)	V_{ss} (l)	Mean residence time (min)	$AUC(0, \infty)$ ($\text{mg l}^{-1} \text{h}$)
Placebo	26.1 $\pm$ 6.5	12.8 $\pm$ 4.6	25.7 $\pm$ 6.4	21.4 $\pm$ 5.3	17.4 $\pm$ 1.3	63 $\pm$ 6	7.2 $\pm$ 0.9	73 $\pm$ 7	881 $\pm$ 141
Paracetamol	36.4 $\pm$ 14.1*	14.6 $\pm$ 3.1	36.6 $\pm$ 13.4	24.8 $\pm$ 6.5	12.0 $\pm$ 1.3**	72 $\pm$ 22	7.8 $\pm$ 1.6	84 $\pm$ 23	923 $\pm$ 159
Indomethacin	32.5 $\pm$ 14.2	16.1 $\pm$ 6.4	32.7 $\pm$ 13.9	21.0 $\pm$ 7.6	18.2 $\pm$ 2.3	79 $\pm$ 17	8.3 $\pm$ 1.1	92 $\pm$ 18	956 $\pm$ 191

* $P = < 0.05$ compared with placebo, ** $P = < 0.001$ compared with placebo and indomethacin.

respectively and the corresponding 0 to 2 h recoveries of inulin were 76 ± 6 , 74 ± 11 and $74 \pm 10\%$.

An unexpected finding was that paracetamol significantly reduced the urinary excretion of acetylated PAH (Table 6). During treatment with paracetamol 69.9 ± 17.5 mg was recovered in 8 h compared with 109.9 ± 22.9 and 114.4 ± 26.7 mg with placebo and indomethacin respectively ($P < 0.001$).

Discussion

Paracetamol produced a significant reduction in the urinary excretion of prostaglandin E_2 which was more marked on the third than on the second day of treatment. This was associated with a significant decrease in sodium excretion and a delay in the onset of diuresis after an acute water load. Indomethacin had generally similar effects, but there appeared to be quantitative differences between the two drugs. Although indomethacin reduced prostaglandin E_2 excretion to a greater extent than paracetamol it did not have a greater inhibitory effect on sodium excretion and it had less initial anti-diuretic action. Paracetamol had no effect on plasma renin activity while in comparison indomethacin produced a significant decrease under basal conditions. The urinary excretion of prostaglandin E_2 largely reflects its renal synthesis and inhibition by non-steroidal anti-inflammatory drugs impairs sodium and water excretion, and reduces plasma renin activity (Carmichael & Shankel, 1985). This mechanism presumably accounts for the effects observed with paracetamol but it is not clear why these should differ from those produced by indomethacin. The urinary excretion of prostaglandin 6-keto $F_{1\alpha}$ (a stable metabolite of prostacyclin or PGI_2) was reduced only modestly by paracetamol and indomethacin on the third day of treatment. However, as with prostaglandin E_2 , its excretion was correlated with sodium output and urine volume following the acute water load. These findings are consistent with the reported natriuretic action of prostacyclin (Angeli *et al.*, 1988).

Little is known of the effects of paracetamol on prostaglandins in man and reports are contradictory. Thus according to Grn *et al.* (1988), it reduced the *in vivo* synthesis of prostacyclin to a much greater extent than in the present investigation while in another study it appeared to have an opposite effect as it inhibited platelet aggregation *in vitro* by a mechanism involving arachidonic acid metabolism (Dupin *et al.*,

1988). The effects of paracetamol on renal prostaglandins in man have not been described previously, but in animals it produces reversible, dose-dependent inhibition of renal medullary prostaglandin E_2 synthesis by a direct action on cyclooxygenase without prior metabolic activation (Mattammal *et al.*, 1979; Zenser *et al.*, 1978). Haylor (1980) reported a reduction in urine volume, sodium excretion and osmolal output in six normally hydrated female subjects following administration of 1.5 g of paracetamol, but prostaglandins were not measured and the sodium intake was not controlled. In another report, paracetamol apparently reduced urine volume, urine osmolality and free water clearance in three patients with nephrogenic diabetes insipidus (Nusynowitz & Forsham, 1966). No information is available concerning the effects of normal doses of paracetamol on plasma renin activity. Wilkinson *et al.* (1979) reported an increase in some patients with paracetamol overdose but this was probably related to the onset of acute renal failure.

Prostaglandin E_2 is a potent renal medullary vasodilator but under normal conditions it does not play an important role in the maintenance of renal blood flow. However, a deficiency in the presence of reduced perfusion or volume or sodium depletion may cause a fall in the glomerular filtration rate and renal blood flow (Garella & Matarese, 1984). Neither paracetamol nor indomethacin reduced the glomerular filtration rate or renal blood flow as measured by the renal clearances of inulin, creatinine and PAH. The lack of effect in these healthy young subjects is not surprising. Although their intake of sodium was restricted, steady state was not achieved as its excretion was still declining on the last day with placebo treatment. The single injection method used for measurement of inulin and PAH clearances has the advantage that fluid loading is not necessary and this is clearly important in studies of the effects of analgesic drugs on renal function.

Treatment with paracetamol and indomethacin was associated with minor increases in the plasma half-life, AUC, volume of distribution and mean residence time of inulin and PAH. Although most of these changes did not reach statistical significance, overall they are consistent with some degree of volume expansion and slower elimination of inulin and PAH. Paracetamol produced a significant decrease in the total body clearance of PAH with a corresponding increase in its half-life. PAH is normally excreted very rapidly but 15 to 20% is acetylated (McAuslane *et al.*, 1987). Paracetamol inhibited the acetylation of PAH since it reduced the

urinary excretion of the metabolite while the recovery of total PAH was unchanged. The reduced total body clearance and increased half-life of PAH during treatment with paracetamol can therefore be largely attributed to its reduced metabolic clearance. This interaction with paracetamol has not been described before and the mechanism is unknown.

The present findings are surprising because with normal use paracetamol does not appear to share the adverse renal effects of the non-steroidal anti-inflammatory drugs. Despite a high degree of suspicion and extensive use over the years even in high risk patients, there have been few clinical reports of nephrotoxicity, and fluid and sodium retention have not been described. Paracetamol might be expected to antagonise the effects of diuretics and anti-hypertensive drugs (Oates, 1988). It has been reported to decrease frusemide-induced natriuresis and diuresis (Abrams *et al.*, 1986), but unlike ibuprofen it did not increase the blood pressure in patients with hypertension (Radack *et al.*, 1987). As with other non-steroidal anti-inflammatory drugs, paracetamol may cause acute renal failure following overdose (Prescott, 1983), and there has been a single report of reversible acute tubular necrosis attributed to the use of therapeutic doses (Gabriel *et al.*, 1982). There have been very few reports of analgesic nephropathy associated with paracetamol alone (Prescott, 1982; Segasothy *et al.*, 1988) and its cumulative consumption during chronic use in patients with arthritis was not related to impairment of renal function (Edwards *et al.*, 1971). The results of recent epidemiological studies have been conflicting. Murray *et al.* (1983) could find no association between paracetamol consumption and end-stage renal disease but Sandler *et al.* (1989) have claimed that the daily use of paracetamol significantly increases the risk of chronic renal disease. However, in the latter study proper information about paracetamol use was not provided, drug histories in most cases were obtained retrospectively by proxy and there was no confirmation of the renal diagnosis.

Recent interest in the renal effects of paracetamol has been directed largely towards the potential for toxicity caused by glutathione-dependent covalent binding following its metabolic activation by cortical cytochrome P-450 and medullary prostaglandin endoperoxide synthetase (Harvison *et al.*, 1988; McMurtry *et al.* 1978; Mohandas *et al.*, 1984). These mechanisms may be relevant to tubular necrosis after acute overdose, but they are unlikely to apply within the therapeutic dose range. Further

studies are required to establish the time course and clinical significance of the effects of normal doses of paracetamol on prostaglandins and renal function.

We gratefully acknowledge technical assistance given by Mr J. Cowie, Mr K. Marwick and Ms W. Barron.

References

- Abrams, S. M. L., Jackson, S. H. D., Johnston, A. & Turner, P. (1986). Does paracetamol modify furosemide diuresis? *Br. J. Pharmacol.*, **89**, 718P.
- Angeli, P., Gatta, A., Caregaro, L., Menon, F., Sacerdoti, D., Merkel, C., Visonà, A., Lusiani, L. & Pagnan, A. (1988). Effects of iloprost, a prostacyclin analog derivative, on renal plasma flow, renal function, and renin-aldosterone system in humans. *Clin. Pharmacol. Ther.*, **44**, 211–216.
- Blackshear, J. L., Napier, J. S., Davidman, M. & Stillman, M. T. (1985). Renal complications of non-steroidal antiinflammatory drugs: identification and monitoring of those at risk. *Seminars in Arthritis and Rheumatism*, **14**, 163–175.
- Carmichael, J. & Shankel, S. W. (1985). Effects of nonsteroidal anti-inflammatory drugs on prostaglandins and renal function. *Am. J. Med.*, **78**, 992–1000.
- Dawborn, J. K. (1965). Application of Heyrovsky's inulin method to automatic analysis. *Clin. Chim. Acta*, **12**, 63–66.
- Dupin, J.-P., Gravier, D., Casadebaig, F., Boisseau, M. R. & Bernard, H. (1988). *In vitro* antiaggregant activity of paracetamol and derivatives. *Thrombosis Research*, **50**, 437–447.
- Edwards, O. M., Edwards, P., Huskisson, E. C. & Taylor, R. C. (1971). Paracetamol and renal damage. *Br. med. J.*, **2**, 87–89.
- Freestone, S., McAuslane, J. A. N., Mackay, I. G., Cowie, J., Watson, M. L. & Prescott, L. F. (1986). Inulin clearance after single intravenous injection: a re-evaluation. *Br. J. clin. Pharmacol.*, **21**, 97P.
- Gabriel, R., Caldwell, J. & Hartley, R. B. (1982). Acute tubular necrosis, caused by therapeutic doses of paracetamol? *Clin. Nephrol.*, **18**, 269–271.
- Garella, S. & Matarese, R. A. (1984). Renal effects of prostaglandins and clinical adverse effects of non-steroidal anti-inflammatory agents. *Medicine*, **63**, 165–181.
- Grøen, K., Drvota, V. & Vesterqvist, O. (1989). Pronounced reduction of *in vivo* prostacyclin synthesis in humans by acetaminophen (paracetamol). *Prostaglandins*, **37**, 311–315.
- Haber, E., Koerner, T., Page, L. B., Kliman, B. & Purnode, A. (1969). Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J. clin. Endocr. Metab.*, **29**, 1349–1355.
- Harvison, P. J., Egan, R. W., Gale, P. H., Christian, G. D., Hill, B. S. & Nelson, S. D. (1988). Acetaminophen and analogs as cosubstrates and inhibitors of prostaglandin H synthase. *Chem. Biol. Interactions*, **64**, 251–266.
- Haylor, J. (1980). Prostaglandin synthesis and renal function in man. *J. Physiol.*, **298**, 383–396.
- Kimberly, R. P., Sherman, R. L., Mouradian, J. & Lockshin, M. D. (1979). Apparent acute renal failure associated with therapeutic aspirin and ibuprofen administration. *Arthritis Rheum.*, **22**, 281–285.
- Levin, M. L. (1988). Patterns of tubulo-interstitial damage associated with nonsteroidal antiinflammatory drugs. *Seminars in Nephrology*, **8**, 55–61.
- Mattammal, M. B., Zenser, T. V., Brown, W. W., Herman, C. A. & Davis, B. B. (1979). Mechanism of inhibition of renal prostaglandin production by acetaminophen. *J. Pharmacol. exp. Ther.*, **210**, 405–409.
- McAuslane, J. A. N., Freestone, S., Barron, W. & Prescott, L. F. (1987). Disposition and kinetics of PAH following a single intravenous injection: measurement of renal plasma flow. *Br. J. clin. Pharmacol.*, **24**, 277P.
- McMurtry, R. J., Snodgrass, W. R. & Mitchell, J. R. (1978). Renal necrosis, glutathione depletion, and covalent binding after acetaminophen. *Toxicol. appl. Pharmacol.*, **46**, 87–100.
- Mohandas, J., Marshall, J. J., Duggin, G. G., Horvath, J. S. & Tiller, D. J. (1984). Differential distribution of glutathione and glutathione-related enzymes in rabbit kidney. *Biochem. Pharmacol.*, **33**, 1801–1807.
- Murray, T. G., Stolley, P. D., Anthony, J. C., Schinnar, R., Hepler-Smith, E. & Jeffreys, J. L. (1983). Epidemiological study of regular analgesic use and end-stage renal disease. *Arch. Intern. Med.*, **143**, 1687–1693.
- Nusynowitz, M. L. & Forsham, P. H. (1966). The antidiuretic effect of acetaminophen. *Am. J. med. Sci.*, **252**, 429–435.
- Oates, J. (1988). Antagonism of antihypertensive drug therapy by nonsteroidal anti-inflammatory drugs. *Hypertension*, **11** (Suppl. II), II4–II6.
- Powell, W. S. (1980). Rapid extraction of oxygenated metabolites of arachidonic acid from biological samples using octadecylsilyl silica. *Prostaglandins*, **20**, 947–956.
- Prescott, L. F. (1982). Analgesic nephropathy: a re-assessment of the role of phenacetin and other analgesics. *Drugs*, **23**, 75–149.
- Prescott, L. F. (1983). Paracetamol overdose: pharmacological considerations and clinical management. *Drugs*, **25**, 290–314.
- Radack, K. L., Deck, C. C. & Bloomfield, S. S. (1987). Ibuprofen interferes with the efficacy of antihypertensive drugs. *Ann. Intern. Med.*, **107**, 628–635.

- Sandler, D. P., Smith, J. C., Weinberg, C. R., Buckalew, V. M., Dennis, V. W., Blythe, W. B. & Burgess, W. P. (1989). Analgesic use and chronic renal disease. *New Engl. J. Med.*, **320**, 1238–1243.
- Segasothy, M., Suleiman, A. B., Puvaneswary, M. & Rohana, A. (1988). Paracetamol: a cause for analgesic nephropathy and end-stage renal disease. *Nephron*, **50**, 50–54.
- Wilkinson, R., James, O. F. W., Roberts, S. H., Morley, A. R. & Robson, V. (1979). Plasma renin activity during the development of paracetamol (acetaminophen) induced acute renal failure in man. *Clin. Nephrol.*, **11**, 196–201.
- Zenser, T. V., Mattammal, M. B., Herman, C. A., Joshi, S. & Davis, B. B. (1978). Effect of acetaminophen on prostaglandin E₂ and prostaglandin F_{2α} synthesis in the renal inner medulla of rat. *Biochim. Biophys. Acta*, **542**, 486–495.

(Received 8 August 1989,
accepted 7 December 1989)