Effects of sulindac on renal function and prostaglandin synthesis in patients with moderate chronic renal insufficiency

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Summary

1. The renal effects of therapeutic doses of sulindac were studied in nine patients with stable renal insufficiency, mean creatinine clearance 37.0 ± 2.2 ml min⁻¹ 1.73 m⁻² (range 24.7–54.6 ml min⁻¹ 1.73 m⁻²).

2. Nine days' treatment with sulindac produced a small, but significant, reduction in the mean creatinine clearance (37.0 ± 2.2 to 34.7 ± 2.2 ml min⁻¹ 1.73 m⁻²; \(P<0.02\)) and ⁹⁹ᵐTc diethylenetriaminepenta-acetate (DTPA) clearance (35.5 ± 3.4 to 31.4 ± 3.6 ml min⁻¹ 1.73 m⁻²; \(P<0.02\)) without altering body weight, effective renal plasma flow \(^{[13]}\)hippuran clearance), plasma renin activity (PRA), 24 h urinary volume or electrolyte excretion.

3. After discontinuation of sulindac, creatinine clearance returned to pretreatment values.

4. In five female patients, pretreatment urinary excretion of the 6-ketoprostaglandin F₁₆ (6-keto-PGF₁₆), a stable breakdown product of prostacyclin (PGI₂), was significantly reduced \((P<0.02)\) when compared with four healthy controls, whereas prostaglandin E₂ (PGE₂) was unchanged. Administration of sulindac did not significantly alter the excretion rate of PGE₂ or 6-ketoPGF₁₆ in this group of patients.

5. In chronic renal disease with moderate renal impairment, reduced renal prostacyclin synthesis may be an important predisposing factor to the renal toxicity associated with the use of non-steroidal anti-inflammatory drugs (NSAID). Short term use of sulindac in therapeutic doses does not appear to influence the excretion of prostaglandins and produces only a minor reversible change in renal function; used cautiously it may have advantages over other NSAID in these patients.-

Key words: chronic renal insufficiency, kidney, prostaglandins, renin, sulindac.

Abbreviations: DTPA, diethylenetriaminepenta-acetate; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drugs; PG, prostaglandin; PRA, plasma renin activity; RBF, renal blood flow.

Introduction

Many adverse renal effects have been reported in association with the use of non-steroidal anti-inflammatory drugs: acute renal failure, chronic renal injury, nephrotic syndrome and interstitial nephritis \([1, 2]\). Of these, the reversible acute renal failure syndrome is most commonly recognized. This is rare in normal healthy individuals \([3, 4]\), but occurs most frequently in clinical situations in which renal function is dependent on local prostaglandin synthesis. The kidney is extremely active in the synthesis of prostaglandins, which influence a variety of its physiological functions, including regulation of renal blood flow (RBF), glomerular filtration rate (GFR) and the urinary excretion of electrolytes and water \([1, 2]\). Renal prostaglandins are particularly important in the maintenance of renal function in conditions associated with potential renal ischaemia; in these
circumstances their synthesis is increased dramatically so as to oppose vasoconstrictive stimuli [1, 5]. The suppression of cyclo-oxygenase, a major enzyme in the biosynthesis of prostaglandins [6], results in impairment of these vital homeostatic processes. The patients at risk are those with either renal insufficiency [9, 10–13] or with hypertension (hypervolaemia, congestive cardiac failure [7] and cirrhosis [8]).

All NSAID inhibit cyclo-oxygenase, but the sensitivity of different tissue to each drug may vary. Aspirin [10, 11], indomethacin [9, 12], naproxen, ibuprofen and fenoprofen reduce both renal function and urinary prostaglandins excretion [14]. So far, sulindac is the only NSAID found not to inhibit renal cyclo-oxygenase significantly [15–17].

The purpose of this study is to determine the basal urinary excretion of prostaglandins in a group of patients with moderately impaired GFR (endogenous creatinine clearance 24.7–54.6 ml min⁻¹ 1.73 m⁻²) and observe the effects of sulindac on renal function and prostaglandin synthesis.

Subjects and methods

Nine patients were studied, four male, five female, aged 35–45 years (mean 43.9 years) with established chronic renal insufficiency for a mean duration of 8.2 years (range 2–18 years). They all had clinically stable renal function (creatinine clearance 24.7–54.6 ml min⁻¹ 1.73 m⁻²) for at least 3 months before the study. All were hypertensive and required one or more antihypertensive agents (seven, β-blockers; six, thiazide diuretics) to maintain satisfactory blood pressure control; drug doses had been unaltered for at least 6 weeks before study. None had a history of congestive cardiac failure, gastrointestinal disorder, bleeding diathesis or allergy to NSAID. Diet was unrestricted and maintenance antihypertensive therapy was continued. Weekly endogenous creatinine clearance estimation, for 3 consecutive weeks immediately before study, confirmed relatively constant renal function in each patient. The study was approved by the Ethical Committee of the Central Manchester Health Authority and informed written consent was obtained from every patient.

All patients were admitted to hospital for renal function assessment 2 days before and 9 days after treatment with sulindac (200 mg twice daily). On each occasion, two consecutive 24 h urine collections and daily venous blood samples were obtained for sodium, potassium, protein, creatinine and creatinine clearance determination. The intra-subject coefficients of variation for creatinine and creatinine clearance were 6.5% and 8.6%, respectively. On the second day urine was collected for 3 h after the patients had completely emptied the bladder on waking, in the morning, for prostaglandins estimation. The volume of urine was recorded and a 20 ml aliquot was frozen immediately to −20°C until assay. On the same day, GFR and effective renal plasma flow (ERPF) were determined simultaneously in the supine position by ⁹⁹ᵐTc DTPA and [¹³¹]hippuran clearance respectively, and a venous blood sample was obtained for plasma renin activity (PRA) after 3 h ambulation.

Two weeks after discontinuation of sulindac, the serum creatinine and endogenous creatinine clearance were assessed on 2 consecutive days.

Urine was also collected, for measurement of urinary PGE₂ and 6-ketoPGF₁α, from four healthy female (aged 24–49 years) subjects. The time and duration of collection were identical to those of the patients under study.

Analysis

Serum and urinary sodium and potassium were measured by flame photometry and creatinine by the Jaffe chromogen reaction, using the Vickers M300 analyser. Urinary protein was estimated by a sulphasalicylic acid turbidity method. ⁹⁹ᵐTc DTPA and [¹³¹]hippuran clearances were determined simultaneously with a single injection technique [18]. All clearance values were corrected for body surface area. PRA was measured by radioimmunoassay of angiotensin I liberated during incubation of plasma at pH 5.75 and 37°C [19]. EDTA and phenylmethylsulphonyl fluoride inhibitors were employed. The between-batch coefficient of variation of the assay was 9.8% at a PRA of 5.5 pmol of ANG I h⁻¹ ml⁻¹.

Prostaglandins assay

Urinary PGE₂ and 6-ketoPGF₁α were measured by radioimmunoassay as described previously [20, 21]. Briefly, 2 ml aliquots of urine were extracted and assayed. An extraction marker (2.5 nCi of [³H]PGE₂, 120–170 Ci/mmol, or 2.5 nCi of [³H]6-ketoPGF₁α, 120–180 Ci/mmol) was incorporated in the aliquot before commencement of extraction procedure. The urinary prostaglandins were extracted into ethyl acetate/propan-2-ol/0.1 mol/litre HCl (3:3:1, by vol.), E and F series prostaglandins were separated from each other and from other prostaglandins by chromatography on silicic acid columns, using 60–200 mesh silicic acid (SIL-A-200, Sigma Chemical Co.; 0.25 g). The samples were evaporated to dryness
under nitrogen and subsequently subjected to radioimmunoassay. The overall recovery for PGE$_2$ and 6-ketoPGF$_{1α}$ was found to be similar (70%).

The radioimmunoassay procedure used a highly sensitive PGE$_2$ antiserum (Miles-Yeda Ltd, Rehovot, Israel), capable of detecting 30 fmol of prostaglandins per tube. For 6-ketoPGF$_{1α}$ assay, antiserum was obtained from New England Nuclear (Dreieich, FRG).

**Statistical methods**

Results are expressed as means ± SEM. The significances of differences between groups were assessed by Student’s paired and unpaired t-tests as appropriate.

**Results**

**Renal function**

During the administration of sulindac there were small, but statistically significant, falls in the mean creatinine (37.0 ± 2.2 to 34.7 ± 2.2 ml min$^{-1}$ 1.73 m$^{-2}$; $P<0.02$) and $^{99m}$Tc DTPA clearances (35.5 ± 3.4 to 31.4 ± 3.6 ml min$^{-1}$ 1.73 m$^{-2}$; $P<0.02$), and a corresponding rise in the mean serum creatinine (195.8 ± 19.7 to 208 ± 18.5 μmol/l; $P<0.02$). Mean $[^{131}]$hippuran clearance (ERPF) increased from 124.9 ± 14.4 to 134 ± 14.7 ml min$^{-1}$ 1.73 m$^{-2}$, but this was not statistically significant (Fig. 1).

Two weeks after discontinuation of sulindac, the serum creatinine and endogenous creatinine clearance had returned to pretreatment values (196.9 ± 21.2 μmol/l and 39.8 ± 3.1 ml min$^{-1}$ 1.73 m$^{-2}$ respectively).

**Urinary prostaglandins**

Since the urinary excretion rate of PGE$_2$ and 6-ketoPGF$_{1α}$ is a valid index of the renal prostaglandins synthesis in female patients only [22], the results of five female patients are presented here.

Before sulindac therapy, the mean basal urinary excretion of PGE$_2$ in female patients was not significantly different from the four healthy women (47.2 ± 13.6 versus 30.85 ± 6.7 ng/h), whereas the urinary excretion of 6-ketoPGF$_{1α}$, the hydrolysis product of prostacyclin, was significantly lower (19.6 ± 8.7 versus 45.86 ± 5.86 ng/h; $P<0.02$).

The change in mean excretion rate of urinary PGE$_2$ (47.2 ± 13.6 to 35.1 ± 15.7 ng/h) and 6-ketoPGF$_{1α}$ (19.6 ± 8.7 to 13.3 ± 8.2 ng/h) was not significant during sulindac therapy, but a wide interpatient variation was noted. No significant correlation was observed between individual changes in clearance values and urinary prostaglandin excretion. The urine flow rate was similar before and during sulindac therapy (51 ± 6.3 and 54 ± 8.0 ml/h; NS).

**Renin levels**

The results of ambulant PRA were available in seven patients. The mean pretreatment PRA was 2.86 ± 0.55 pmol of ANG I h$^{-1}$ ml$^{-1}$ compared with 3.83 ± 0.33 pmol of ANG I h$^{-1}$ ml$^{-1}$ in normal subjects ($n = 20$). Administration of sulin-
Sulindac was not associated with any significant change in the mean PRA (2.86 ± 0.55 to 1.80 ± 0.55 pmol of ANG I h⁻¹ ml⁻¹; NS). However, a sharp fall in PRA was observed in three out of five patients receiving β-blocker and sulindac concurrently (3.3 ± 0.1 to 0.9 ± 0.3 pmol of ANG I h⁻¹ ml⁻¹; P < 0.02). The urinary sodium excretion (U Na⁺/V Na⁺) was not significantly altered (143.8 ± 23.4 to 153.2 ± 22.2 mmol/24 h; NS) during the treatment.

**Blood pressure, body weight and electrolytes**

Sulindac administration was not associated with any significant change in the systolic (137 ± 5.0 to 141 ± 6.0 mmHg; NS) or diastolic (88 ± 3.0 to 89 ± 2.0 mmHg; NS) blood pressure, body weight (68.1 ± 5.1 to 68.0 ± 5.0 kg; NS), urine output (1.94 ± 1.9 ± 0.22 litres/24 h; NS) or concentrations of serum or urinary electrolytes.

**Discussion**

Blum *et al.* demonstrated increased excretion of urinary PGE₂ in stable chronic renal insufficiency (mean creatinine clearance 20–59 ml/min), suggesting an important homoeostatic role for intrarenal PGE₂ [23]. We were unable to confirm this observation in a group of patients with similar renal impairment, but found significantly reduced levels of 6-ketoPGF₁α. This agrees with the findings of Ciabattoni *et al.* and supports the view that in chronic renal insufficiency maintenance of renal function is likely to be dependent on synthesis of the potent vasodilator PGІ₂, and that reduced excretion of 6-ketoPGF₁α may represent an important risk factor in NSAID-induced renal toxicity [17].

In these situations the use of sulindac may be advantageous, compared with other NSAID, as it preferentially spares renal cyclo-oxygenase inhibition [15]. In the recent study by Ciabattoni *et al.*, sulindac given in therapeutic doses for 1 week to patients with mild renal impairment (mean creatinine clearance 90 ± 21 ml min⁻¹ 1.73 m⁻²) did not alter renal function or urinary excretion of prostaglandins [17]. In our study, similar doses of sulindac given to patients with moderately impaired renal function (mean creatinine clearance 37 ± 2.5 ml min⁻¹ 1.73 m⁻²) produced a small, but significant, fall in GFR without affecting ERPF or urinary excretion of prostaglandins. In all patients GFR invariably returned to pretreatment values after withdrawal of sulindac therapy, suggesting a causal relationship.

Although the exact mechanisms responsible for a fall in renal function remain uncertain, it is important to note that our patients had more advanced renal impairment and were receiving maintenance antihypertensive therapy. Both of these factors may be relevant in influencing the intrarenal haemodynamics, or pharmacokinetics of sulindac, such that it renders renal cyclo-oxygenase susceptible to inhibition. It is surprising, however, that an associated fall in urinary excretion of prostaglandins did not occur. This probably reflects either the small number of patients studied or a minor change in intrarenal prostaglandin levels, which, although sufficient to influence cortical function, are quantitatively too small to affect the urinary excretion rate. It is of interest to note that a sharp fall in PRA was observed only in those patients receiving β-blocker and sulindac concurrently, suggesting an inhibition of prostaglandin mediated release of renin [24] by sulindac. Alternatively, sulindac alone or as a result of interaction with concurrent antihypertensive therapy may exert a direct effect on the renal function, by a mechanism independent of cyclo-oxygenase inhibition.

Whatever the mechanism, it is important to emphasize that even in the presence of multiple risk factors the short term use of sulindac in therapeutic doses produced a reversible fall in GFR of only 11% compared with 35% and 58% with indomethacin [12] and aspirin [2, 10] respectively, as reported in other series. The comparison of sulindac and non-selective NSAID, such as aspirin or indomethacin, in our patients would have been interesting, but in the presence of overwhelming evidence of the deleterious effect of these non-selective cyclo-oxygenase inhibitors at this level of GFR, with a definite risk of precipitating an acute renal failure [11, 13], such comparison was considered to be ethically unjustifiable.

We believe our findings may have practical significance in the management of patients with moderately impaired renal function, who are frequently hypertensive and often require multiple antihypertensive therapy to maintain stable renal function. In this clinical setting, reduced intrarenal prostacyclin synthesis may be an important risk factor to NSAID therapy and, although no NSAID should be regarded as completely safe, sulindac in therapeutic doses appears to influence renal function only marginally; used cautiously, it may have advantages over other NSAID in such patients.

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References


