Renal impairment associated with non-steroidal anti-inflammatory drugs

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SUMMARY We have compared the renal function on admission and discharge of 22 patients routinely admitted to our rheumatology ward. None had previously diagnosed renal failure. Of 11 patients in whom we stopped long term non-steroidal anti-inflammatory drug (NSAID) therapy, all showed a rise in creatinine clearance (Ccr) after three to 28 days. In contrast, a control group comprising 11 similar patients who continued to receive NSAIDs showed no significant change. Recent work has suggested that it is possible to identify patients at risk of developing nephrotoxic side effects with NSAIDs. Based on these criteria (but excluding age alone as a risk), six patients from the first group and 10 from the second group would have been without risk. We infer from this that asymptomatic, reversible impairment of renal function is common, and that the potential clinical benefit from the use of NSAIDs should be balanced against this predictable toxicity.

Key words: renal failure, arthritis rheumatoid, analgesia anti-inflammatory.

All NSAIDs currently available are potent inhibitors of cyclo-oxygenase, an enzyme needed for the production of prostaglandins from arachidonic acid. This is thought to explain their anti-inflammatory actions.^{1,2} Prostaglandins are, however, ubiquitous and, though their functions are only partly understood, it is accepted that NSAID suppression of their production may be responsible for some of the side effects associated with NSAID use. Specifically, in the kidney, ischaemic stress is compensated for by an increased production of vasodilatory prostaglandins (PGE₂/PGI₂) to maximise cortical blood flow. Administration of NSAIDs to patients dependent on prostaglandins for maintenance of their renal blood flow produces a fall in urinary prostaglandins, with a subsequent reduction in glomerular filtration.^{3,4} Groups of patients 'at risk' in this respect have been described.^{5,6} These include patients with renal failure, systemic lupus erythematosus, congestive cardiac failure, hepatic cirrhosis, extracellular fluid volume contraction (e.g., secondary to diuretic administration), and the elderly. Patients without such associated risk factors are

considered exempt from this effect, though still vulnerable to apparently more idiosyncratic reactions.^{7,8} Renal papillary necrosis, interstitial nephritis/fibrosis, focal/mesangial proliferative glomerulonephritis, and the nephrotic syndrome have all been associated with NSAIDs.^{8,9}

Previous studies attempting to define the effect of NSAIDs on renal function fall under two headings. The first, appropriate to the assessment of a novel NSAID, usually involves the monitoring of renal function for a period of weeks or months after initiation of therapy. Serum creatinine and urea are the usual indices of renal function examined. Such studies report a low incidence of renal problems.¹⁰ The second, appropriate to defining the effect that NSAIDs have on inducing renal failure, examines the incidence of NSAID prescription in patients presenting with renal failure.⁸

Neither type of study provides a clear picture of the incidence of asymptomatic NSAID induced renal suppression. A recent study of the second design leads the authors to speculate that 'the pattern of renal disease associated with NSAIDs may be more extensive than previously recognised'.⁸

In an attempt to test this hypothesis we have assessed renal function in two groups of patients routinely admitted to our rheumatology ward. In

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Table 1 NSAID/diuretic history, age, and diagnosis of patients in whom assessments of renal function were compared on admission and after cessation of NSAIDs (group 1)

Patient No	Diagnosis*	Age (years)	NSAID	Diuretics	Days not receiving NSAIDs‡
1	RA	69	Azapropazone	No	36
2	RA	69	Indomethacin	No	8
3	RA	72	Azapropazone	No	32
4	RA	59	Naproxen	No	34
5	RA	64	Diclofenac	No	14
6	RA	39	Piroxicam	No	3
7	RA	64	Ketoprofen	Bendrofluazide‡	32
8	OA	86	Indomethacin	Frumil§	12
9	RA/DM/H	74	Aspirin	No	18
10	OA	68	Mefenamic acid	Frumil	12
11	CAP/DM	59	Azapropazone	No	12

*RA=rheumatoid arthritis; OA=osteoarthritis; DM=diabetes mellitus; H=hypertensive; CAP=capsulitis.

‡This indicates the intervals between renal assessment for each patient.

§Prescribed for heart failure.

||Frusemide 40 mg/amiloride hydrochloride 5 mg; prescribed for breathlessness.

||Prescribed for ankle swelling.

one group we have withdrawn long term NSAID medication and serially measured serum urea, creatinine, and 24 hour creatinine clearances (Ccrs) for as long as they were symptomatically controlled on simple analgesia. This group has been compared with a population in whom NSAIDs were maintained.

Patients, methods, and results

Group one consisted of 11 patients admitted to our

ward (patients 1–11, Table 1) who had all received NSAIDs for at least six months. Their age range was wide (39–86 years, mean 66), eight had ‘classical rheumatoid arthritis’ (RA), two osteoarthritis (OA), and one capsulitis (CAP). The five elderly patients could have been said to have been at risk.^{5,6} Three patients were receiving diuretics and two had non-insulin dependent diabetes mellitus (DM), one of whom was hypertensive (H). NSAID medication was discontinued, but administration of all other

Fig. 1 Change in serum creatinine, urea, and 24 hour creatinine clearances when receiving NSAIDs (ON) and at the maximum interval after their discontinuation (OFF). Patient Nos 1–11, group 1.

Table 2 NSAID/diuretic history, age, and diagnosis of patients serially assessed throughout admission without any change in their medication (group 2)

Patient No	Diagnosis	Age (years)	NSAID	Diuretics	Length of stay (days)
12	Seroneg. RA	74	Flurbiprofen	No	22
13	RA	40	Sulindac	No	22
14	RA	50	Naproxen + indomethacin	No	33
15	RA/DM	72	Sulindac	No	7
16	RA	54	Piroxicam	No	13
17	RA	59	Indomethacin suppository	No	29
18	RA	45	Indomethacin	No	14
19	RA	72	Aspirin	No	11
20	RA	69	Azapropazone	No	6
21	RA/psoriatic arthropathy	72	Flurbiprofen	No	5
22	RA/OA	62	Naproxen	No	12

medications (including second line antirheumatic agents) continued throughout the study.

Estimations of serum urea and creatinine with 24 hour Ccrs were performed on admission and their various NSAIDs then withdrawn. Paracetamol or diazepam, or both, were given for symptomatic relief. Renal function was assessed again before discharge or reintroduction of their NSAIDs. Measurements of serum urea and creatinine were made with diacetyl monoxime and Jaffe analyses (Vickers SP 120 multichannel analyser).

As our patients were variable in their tolerance to

NSAID withdrawal, some required reintroduction of their drugs before discharge. The mean interval between admission and either discharge or the necessary reintroduction of NSAIDs was 19.4 days.

We compared initial estimations of renal function with those immediately before the reintroduction of NSAIDs or immediately before discharge if the patient did not require another NSAID.

In this group the initial serum creatinine showed a significant fall on withdrawal of NSAIDs (mean (SEM) 103.9 (10.42) $\mu\text{mol/l}$ v 76.2 (9.55) $\mu\text{mol/l}$; $p < 0.02$). The serum urea showed a less consistent

Fig. 2 Change in serum creatinine, urea, and 24 hour creatinine clearances on admission (ADM) and discharge (DIS) of patients whose NSAID medication continued throughout their stay. Patient Nos 12-22, group 2.

trend, which did not reach statistical significance (8.2 (0.86) mmol/l v 6.8 (0.55) mmol/l). All patients showed a rise in Ccr when not receiving NSAIDs (45.6 (5.22) ml/min/1.73 m^2 v 68.8 (6.48); $p < 0.001$). Individual results are illustrated in Fig. 1.

Patients varied greatly as might be expected with such a heterogeneous group, and an increment in Ccr ($>10\%$) was first measurable from two to 28 days after withdrawal.

Group two consisted of 11 patients receiving NSAIDs throughout admission (patients 12–22, Table 2). Their age range was similar (40–74 years, mean 64.9). The mean interval between assessments was comparable with group 1 (15.8 days). One patient was diabetic, none received diuretics. There was no significant change in serum creatinine (mean (SEM) on admission 99.5 (7.18) $\mu\text{mol/l}$ v 100.2 (8.64)), urea (7.2 (0.74) mmol/l v 7.2 (1.07)), or Ccr (54.6 (5.38) ml/min/m^2 v 52.5 (6.14)). Individual results are illustrated in Fig. 2.

Routine urine analysis including microscopy was normal in all patients. All Ccrs were corrected for surface area (per 1.73 m^2), and in two cases the measurements validated by concurrent estimations of chromium ethylenediaminetetra-acetate (Cr EDTA) clearances (Ccr 33, Cr EDTA 31; Ccr 44, Cr EDTA 40).

Quoted statistics use the paired t test.

Discussion

Our series of 11 patients who stopped NSAID medication showed a rise in Ccr mirrored by a fall in serum creatinine. This implies that asymptomatic renal impairment by NSAIDs is common. Three of our patients were under 60 years old without any recognised 'risks'. If, as has been suggested, NSAIDs have no effect on the normal kidney,^{5,11} then this indicates either an alternative mechanism for reversible nephrotoxicity or that our patients do not have normal kidneys.

None of our patients were biopsied, and we know of no comparable studies where histological examination has been performed on patients with mild, presumably prostaglandin mediated, reversible renal failure. Adams *et al* biopsied patients presenting with both acute and chronic renal failure associated with NSAIDs which, though reversible, was biochemically more severe. They found abnormal biopsy specimens in all their patients and reported significant progression of interstitial fibrosis in biopsy specimens from one patient four weeks apart.⁸

We have no evidence that any one NSAID has a greater adverse effect on renal function than another, though sulindac has been claimed to possess less nephrotoxicity.¹² This warrants further investigation. Although recent works suggests that NSAIDs with shorter half lives are theoretically safer when prescribed to populations at risk,⁸ we have noticed no difference in the small groups we have studied. Only long term study of patient groups will show whether this reversible effect is later related to clinically apparent renal failure.

The prescription of NSAIDs would appear unavoidable in rheumatological practice. Recognition of predictable renal toxicity should be balanced against potential clinical efficacy. Where clinical benefit appears to outweigh this risk, renal function should be monitored regularly.

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