NSAIDs and Kidney

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Abstract
NSAIDs are commonly used drugs. Even with the advent of selective COX-2 inhibitors, nephrotoxicity still remains a concern. The adverse effects of NSAIDs are mediated via inhibition of prostaglandin synthesis from arachidonic acid by non-specific blocking of the enzyme cyclooxygenase leading to vasoconstriction and reversible mild renal impairment in volume contracted states. When unopposed, this may lead to acute tubular necrosis and acute renal failure. NSAIDs also produce interstitial nephritis with or without nephrotic syndrome secondary to minimal change disease. Although this presents as acute renal failure, it can progress in some cases to chronic renal failure. Papillary necrosis has been incriminated in the development of chronic renal failure secondary to NSAIDs. In patients on long term NSAIDs without acute or chronic renal failure, subclinical renal dysfunction such as reduced creatinine clearance and impaired urine concentrating ability has been shown to be present. Although this sub-clinical dysfunction is reversible on withdrawal of NSAIDs, some reports have suggested a persistent residual dysfunction. Even with a wide range of NSAIDs at our disposal, a renal safe NSAID is yet to be discovered.

INTRODUCTION
Non steroidal anti-inflammatory drugs (NSAIDs) are amongst the most commonly prescribed medication. Some are available over the counter and likely to be abused. Serious gastrointestinal side effects have been minimized with the advent of selective and specific COX-2 inhibitors and misoprostol. However, the newer NSAIDs continue to be nephrotoxic much like the conventional NSAIDs.1

Nephrotoxicity attributed to NSAIDs has been reviewed in the past.2-8 The spectrum of nephrotoxicity includes acute tubular necrosis, acute tubulointerstitial nephritis, glomerulonephritis, renal papillary necrosis, chronic renal failure, salt and water retention, hypertension, hyperkalaemia and hyperenaemic hypoaldosteronism.9 There are reports of sub-clinical renal dysfunction due to NSAIDs,10 NSAID induced chronic renal failure remains a debatable issue.11

This article reviews relevant English literature on acute and chronic renal failure and sub-clinical renal impairment due to NSAIDs (Medline search from 1990 to 2002 using key words – NSAIDs, acute renal failure, chronic renal failure, interstitial nephritis and subclinical nephrotoxicity)

PATHO-PHYSIOLOGY
Prostaglandins maintain renal blood flow (RBF) and glomerular filtration rate (GFR) especially in fluid depleted states. Locally synthesised prostaglandins PG12 (prostacyclin), PGE2, and PGD2 cause vascular dilatation, diminish vascular resistance and enhance renal perfusion with redistribution of blood flow from the renal cortex to nephrons in the juxta-medullary region.12 PGE2 and to a lesser degree PGF2µ cause diuresis and natriuresis by inhibiting the transport of sodium and chloride in the thick ascending limb of loop of Henle and the collecting ducts.13,14 PGE1 tends to antagonize the action of antidiuretic hormone (vasopressin).15,16 Lastly, prostacyclin in concert with PGE2, serves to maintain the glomerular filtration rate.7

In volume contracted states renin-angiotensin-aldosterone axis is stimulated with increased renin, angiotensin II, and aldosterone production resulting in renal vasoconstriction and increased sodium and chloride reabsorption. There is increased sympathetic outflow, which further increases the vascular tone. In this setting, prostaglandins provide compensatory vasodilatation of renal vascular bed and ensure adequate renal blood supply precluding acute renal functional deterioration. PGE2, PGD2, and to a lesser degree prostacyclin, cause vasodilatation by depressing norepinephrine release. PGE2 antagonizes the vasoconstrictive action of angiotensin II on afferent arterioles.7

EFFECT OF NSAIDs
The side-effects of NSAIDs are the consequence of inhibition of prostaglandin synthesis. This permits unopposed vasoconstrictive action of leukotrienes,
angiotensin II, vasopressin, endothelin and catecholamines. In normal salt and water replete subjects this does not result in reduction of GFR but in states of renal hypoperfusion it can result in acute renal failure (ARF). Additionally NSAIDs produce hyporeninaemia and hypoaaldosteronism. This along with the decreased distal tubular flow and sodium delivery results in hyperkalaemia.\textsuperscript{1}

Conditions predisposing to NSAID induced renal failure include hypovolaemia, congestive cardiac failure, nephrotic syndrome, cirrhosis with ascites, sodium depleted states like chronic diuretic therapy and gastrointestinal losses, pre-eclampsia, glomerulonephritis, urinary tract obstruction, concomitant use of nephrotoxic drugs like cyclosporin A, gentamicin or FK 506, advancing age and chronic renal failure.\textsuperscript{5}

**NSAIDS AND ACUTE RENAL FAILURE**

NSAIDs rank second to aminoglycosides as the most common cause of nephrotoxic ARF. Besides producing a reversible renal failure, NSAIDs are known to cause acute interstitial nephritis with haematuria, proteinuria and flank pain.\textsuperscript{17}

**Incidence** : ARF associated with NSAIDS accounts for 15.5% of all cases of drug induced renal failure.\textsuperscript{18} Most of the literature is as case reports and case series. The few studies that have looked at the incidence of ARF due to NSAIDs have arrived at different conclusions.

Fox et al (1984)\textsuperscript{19} in a retrospective study studied the incidence of rise in serum urea nitrogen in 2 population groups. Group 1 was an in hospital population of 41,418 patients. All instances of drug attributed rises in serum urea nitrogen levels were identified. Of 1,222 NSAID users, 14 (1.1%) had a rise in BUN compared to 505 (1.3%) of the 40,196 patients who had not received NSAIDs. Group 2 was a population of over 55,000 patients seen in the out-patients who had filled one or more prescriptions for NSAIDs. 1% of phenylbutazone users (N = 35,364), 6% of the indomethacin users (N = 22,100) and 22% of ibuprofen users (N = 8412) had filled in more than 5 prescriptions per year (classed as continuous users). None of these patients was hospitalised for ARF.

In contrast, in a case control study (Evans et al 1995) involving a population of 420,600 patients, of the 207 cases of ARF due to various causes, seen over 2 years, recent exposure to NSAIDS and previous exposure to aspirin were independently associated with hospitalisation for ARF with the odds ratio of 2.2 and 2.19 respectively. The authors concluded that there is an approximate doubling of the risk of hospitalisation for ARF with oral NSAIDs. Perez Gutthann et al\textsuperscript{20} in a population based case control study (1996), found that current NSAID users had an adjusted odds ratio for ARF of 4.1 and that the risk of ARF was especially high during the first month of NSAID use (odds ratio 8.5). The users of high daily doses of NSAIDs had an even higher odds ratio (9.8) for the development of ARF.

Griffin et al\textsuperscript{21} studied NSAID induced ARF in elderly persons. They performed a nested case-control study using Tennessee Medicaid enrollees aged ≥65 between 1987-1991. These patients had been hospitalized with community-acquired ARF. Of the 1,799 patients with ARF (4.51 hospitalizations per 1,000 person-years), 18.1% were current users of NSAIDs as compared with 11.3% of 9.899 randomly selected population controls. They concluded that NSAID use resulted in an estimated 25 excess hospitalizations associated with renal failure per 10,000 years of use, representing a relatively uncommon and avoidable cause of ARF in elderly persons.

In another study\textsuperscript{22} of ARF in the elderly of 109 unselected patients with ARF admitted to a nephrology unit during a 30 month period, 39 had drug-related acute renal failure. (NSAIDs 24 patients, ACE inhibitors 8 cases). The mean age of drug induced ARF patients was significantly greater than the remaining ARF patients confirming the high susceptibility of ageing kidneys to nephrotoxic damage caused by drugs affecting glomerular autoregulation by microvascular mechanisms.

**Histopathology (HP)** : ARF secondary to NSAIDs can be the result of multiple mechanisms. Reversible renal insufficiency or functional impairment of renal function is the most common mechanism. Others are acute tubular necrosis (ATN) and acute interstitial nephritis (AIN). Rare mechanisms include acute papillary necrosis and renal vasculitis.\textsuperscript{2}

Adams et al\textsuperscript{23} found ARF in 7 of 17 patients of renal failure who presented to a rheumatology clinic over a 3 year period. ATN was present in 4 while AIN accounted for the remaining. All patients improved on discontinuation of the offending NSAID. Brezin et al\textsuperscript{24} studied 3 cases of NSAID induced ARF in patients with nephrotic syndrome. HP was suggestive of AIN. Azotaemia occurred in the absence of hypertension, rash, fever or eosinophilia. Postishil et al\textsuperscript{25} described pathological findings on renal biopsies from two groups of patients with NSAID induced kidney lesions. In the first group (n=9), patients of different age groups, developed renal disease after short term use of NSAID manifesting clinically with acute renal failure along with allergic manifestations such as skin rash and eosinophilia. Morphological features were those of AIN without glomerular lesions. In the second group (n=23), the disease developed in older patients with compromised renal circulation after long term use of NSAIDs presenting clinically as nephrotic syndrome and morphologically as acute tubulointerstitial nephritis with minimal change lipoid nephrosis. In a study by Warren et al\textsuperscript{26}, 5 out of 55 patients with adult onset minimal change glomerulopathy had NSAID associated minimal change nephropathy. Additionally three of these had interstitial nephritis. Marasco\textsuperscript{27} reported a case of ibuprofen associated reversible ARF with hyperkalaemia, tubular necrosis and proteinuria. Kidney biopsy revealed mesangial hypercellularity without glomerular crescent formation, tubulointerstitial nephritis with focal inflammatory infiltrates of predominantly mononuclear cells and neutrophils as well as focal tubular destruction. Direct immunofluorescence examination showed diffuse mesangial IgM and C3 deposits as well as vascular C3 deposition.
Renal impairment due to NSAID use may manifest as acute renal failure (ARF) or chronic renal failure (CRF). Both can present as acute or chronic and may involve acute tubular necrosis (ATN) or acute interstitial nephritis (AIN) depending on the mechanism of injury. The pathophysiology of NSAID-induced renal impairment is complex and can involve direct tubular toxicity, immunological reactions, or a combination of both. The clinical presentation of ARF due to NSAIDs may include acute tubular necrosis (ATN), acute interstitial nephritis (AIN), or acute nephrotoxic renal failure (AN). The presentation of CRF due to NSAIDs may include chronic interstitial nephritis (CIN) or chronic nephrotoxic renal failure (CN). The clinical presentation of CRF may include chronic interstitial nephritis (CIN) or chronic nephrotoxic renal failure (CN).
maintained by local PG production is decreased by NSAID ingestion. The renal papillary lesion is sharply demarcated. The histology reveals coagulative necrosis consistent with infarction. The necrosis is limited to the distal segment of the involved pyramid. This may be attributed to the maximal urinary concentrating ability displayed by this region of the kidney. In case of ureteric obstruction due to the sloughed papillae, forced diuresis usually results in prompt return of renal function. The long term functional consequences are limited and relate to inability to produce maximally concentrated urine. This type of nephropathy has been reported with fenoprofen, mefanamic acid, ibuprofen and phenylbutazone.\textsuperscript{36-39}

A recent study\textsuperscript{40} investigated the role of FR167653, a p38 mitogen-activated protein kinase (MAPK) in the inflammatory processes of renal ischaemia/reperfusion injury in mice. A large number of infiltrated cells and marked acute tubular necrosis in outer medulla was observed after renal ischaemia/reperfusion injury. FR167653 significantly decreased cell infiltration into outer medulla, and the extent of ATN. FR167653 markedly decreased the transcription of interleukin-1 beta, tumour necrosis factor-alpha, monocyte chemoattractant protein-1 and regulated upon activation and normal T cell expression in diseased kidneys. FR167653 decreased the number of phosphorylated p38 MAPK-positive cells. This suggests that FR167653 markedly ameliorated renal ischaemia/reperfusion injury, possibly by inhibiting cytokine/chemokine expression and consequent phosphorylation of p38 MAPK in renal tissue.

Generalized vasculitis with glomerulonephritis producing ARF has been rarely reported. Two of the 3 reported cases were attributed to piroxicam, one of whom developed the same clinical picture upon rechallenge.\textsuperscript{41} The lesion was reversible in these 2 cases on discontinuation of the drug. The third case due to mefenamate died from disseminated aspergillosis following steroid therapy.\textsuperscript{42}

\textbf{NSAID AND CHRONIC RENAL FAILURE (CRF)}

From the preceding discussion, it is evident that most forms of NSAID induced ARF are reversible. However NSAID related CRF is known. The underlying pathology is chronic papillary necrosis or chronic interstitial nephritis.\textsuperscript{5} In a one year prospective, collaborative study (1986) 14 of 62 patients with analgesic or NSAID induced ARF developed permanent renal damage.\textsuperscript{34} CRF was more frequent in patients who had developed AIN when compared with those who had an episode of ATN. It appears that renal function may not always return to baseline values after an acute episode of interstitial nephritis\textsuperscript{45-44} and interstitial fibrosis may then progress to CRF if NSAID consumption is continued.\textsuperscript{35}

Shwarz et al\textsuperscript{45} studied the outcome of AIN and the risk factors for transition from acute to chronic interstitial nephritis in a retrospective study of 1068 renal biopsies. Patients who developed permanent renal insufficiency after acute interstitial nephritis were compared with those who had reversible renal insufficiency, with respect to the causative agent, the symptoms, and the clinical and histological findings. AIN was found in 69 (6.5%) of all biopsies. In 59 (85%) of these it was drug induced. Analgesics and NSAIDs were responsible for AIN in 16 and 17 cases respectively. Renal insufficiency was reversible in 69% and permanent in 31% (12% partially reversible, irreversible in 19%). Over all drug induced interstitial nephritis caused permanent renal insufficiency in 36%, the figure being 56% in NSAID induced cases. Subacute symptoms and chronic analgesic or NSAID use were related to a more chronic course of interstitial nephritis. Histologically tubular atrophy, interstitial granuloma and pronounced interstitial cell infiltration indicated chronicity.

\textbf{Pathophysiology}

The pathophysiology of CRF and ESRD due to NSAIDs is not entirely clear. Non immunologic and immunologic mechanisms may be involved. Medullary ischaemia seems to be the initiating event. NSAIDs, by inhibiting prostaglandin synthesis reduce medullary blood flow.\textsuperscript{7} Pre-existing analgesic nephropathy\textsuperscript{46} and acute pyelonephritis\textsuperscript{47} seem to favour the development of NSAID induced nephrotoxicity, suggesting that in this setting impaired medullary circulation may play a critical role in inducing papillary necrosis and chronic renal injury. Papillary necrosis may also result from reactive intermediate metabolic products of the drug, deviation of arachidonic acid metabolism pathway\textsuperscript{48} or from the accumulation of phospholipids in the renal papilla\textsuperscript{49} Hypertension may act as an aggravating factor.\textsuperscript{50}

Immunological reactions that develop during the acute phase may continue to operate after the injury. Growth factors, (like TGF-\beta), and cytokines can induce both interstitial fibrosis and hypertrophy of the cells of the interstitium\textsuperscript{51}.

\textbf{INCIDENCE OF CRF AND CLINICAL ASSOCIATIONS}

Although the earlier reports focused on acetaminophen, phenacetin and analgesic mixtures as a cause of CRF, a number of studies have studied the role of aspirin and non aspirin NSAIDs in inducing chronic renal disease. It is difficult to delineate between these compounds as causative agents for CRF, as chronic renal disease occurs in patients with arthritis and other pain syndromes in whom both analgesics and NSAIDs are consumed by the patients at different times during the illness.

Early reports questioned a cause and effect relationship between NSAID use and chronic renal failure. Perneger et al\textsuperscript{52} compared 716 cases of ESRD on dialysis as against 1259 controls and classified them as light, moderate and heavy users of analgesics if they consumed 0-104 pills/year (0-2 pills/week), 105-365 pills/year (1 pill/day) or > 366 pills/year (>1 pill/day) respectively. They found that heavy users of acetaminophen had an increased risk of ESRD whereas moderate use did not increase the risk of ESRD. The odds of ESRD increased with cumulative intake of acetaminophen. High life time intake of NSAIDs was associated with a 4 fold increase in the odds for development of ESRD. Odds of ESRD were low with moderate intake of aspirin or NSAIDs,
suggested that low doses of aspirin and NSAIDs are safe.

Emkey et al studied 46 patients (mostly rheumatoid arthritis) taking aspirin continuously for ten or more years. All creatinine and BUN levels were found to be normal suggesting that long term salicylate ingestion does not cause renal damage. D’Agati reviewed several human studies that addressed the chronic nephrotoxicity of aspirin alone or relative risk of end-stage renal disease in association with aspirin use after correction for other analgesics. With the exception of one case-control study demonstrating a low, but statistically significant risk of end-stage renal disease in association with aspirin use, all other case control studies and several prospective studies were unable to identify a significant risk of chronic renal failure in patients using aspirin.

Murray et al studied 527 cases of ESRD from 18 dialysis units and compared these with 1047 controls randomly selected from hospital admission lists. 12.7% of cases and 12% of controls had at least one period of almost daily use of aspirin, acetaminophen or phenacetin lasting 30 days or longer. They found no significantly increased risk of CRF in patients who had consumed one or more analgesics for more than 3 years when compared with non-users or in those who had consumed >3kg of analgesics (aspirin, phenacetin, acetaminophen or their combinations). They concluded that regular analgesic consumption is not responsible for the majority of patients with ESRD. Combination analgesic use accounted for all or part of the regular analgesic use of 6.8% of the 527 cases and 5.7% of the 1047 controls for periods longer than three year. However, they added that there may be a small but significant risk of ESRD development after the use of large doses. Regular analgesic use may also increase the risk of milder forms of renal failure and may exacerbate existing renal impairment.

Rexrode et al conducted a cohort study of analgesic use data from the Physician’s Health study (1982-1995). A total of 11,032 initially healthy men who provided blood samples and reported analgesic were grouped as never <12 pills, 12-1499 pills; 1500-2499 pills, and ≥2500 pills. 460 men had elevated creatinine levels (4.2%); 1258 had reduced creatinine clearance (11.4%). Mean creatinine levels and creatinine clearances were similar among men who did not use analgesics and those who did, even at total intakes of 2500 or more pills.

But a number of studies have shown that long term use of NSAIDs may indeed lead to CRF. Pommer et al studied 921 patients on dialysis. They found an increased relative risk of ESRD after regular analgesic mixture consumption. Monthly analgesic intake of less than 60 units (i.e. tablets, liquids, suppositories) over at least 5 years resulted in a RR of 2.03, while an intake of more than 60 units led to an increase of RR to 4.83. The risk increased with both the total dose consumed and the exposure time. No increase in relative risk was found with the use of single component analgesics.

Sandler et al compared 709 patients with chronic renal dysfunction (serum creatinine >1.5mg/dl) or renal failure with 717 controls. They observed a two fold increase in the risk of CRF in previous daily users of NSAIDs. The risk factors were age over 65 yrs, presence of heart disease and compromised renal function, diuretics, previous MI, and regular alcohol consumption. In an earlier communication, Sandler et al had reported a higher risk of renal disease in daily users of phenacetin (odds ratio 5.11) and acetaminophen (odds ratio 3.2), but none in daily users of aspirin.

In a recent study by Fored et al (2001), regular use of either aspirin or acetaminophen was associated of a 2.5 fold increase in the risk of CRD. The RR rose with increasing cumulative lifetime doses, more consistently with acetaminophen than with aspirin. The types of renal failure most strongly associated with regular use of acetaminophen in addition to aspirin were renal failure linked to diabetes (odds ratio 2.8), systemic disease or vasculitis (odds ratio 5.1), but estimates of relative risks of approximately 2.0 were found for all types of chronic renal failure.

Segasothy et al studied prospectively the risk of renal papillary necrosis and renal dysfunction due to the chronic use of NSAIDs in 259 heavy analgesic users in the general hospital over an 11 year period. 69 new cases of analgesic nephropathy with renal papillary necrosis were identified. 29 had consumed excessive quantities of NSAIDs alone (17 single NSAID), while 9 had consumed NSAIDs in combination with paracetamol, aspirin, caffeine and/or herbal medications. Renal impairment was noted in 26 of these 38 cases.

In a subsequent study, by Segasothy et al 94 patients with chronic arthritis who had consumed more than 1000 capsules and/or tablets of NSAIDs were subjected to renal profiles, intravenous urography, ultrasonography and CT scan to look for renal papillary necrosis. 10 of the 82 patients who completed the study showed radiological evidence of renal papillary necrosis. Renal impairment was present in 20 patients. The patients had consumed 1000-26,300 capsules and/or tablets over periods ranging from 1-30 years. They concluded that patients with arthritis who consume excessive amounts of NSAIDs are at risk of developing renal papillary necrosis and chronic renal insufficiency.

Kantachuesiri et al studied heavy analgesic abuse in 84 patients with chronic tubulointerstitial nephritis with 2 control groups; i) 192 selected from hospitalized patients without renal disease and ii) 166 relatives or friends visiting the hospitals. On multiple logistic regression analysis, patients whose estimated lifetime use of acetaminophen was 1000g or more had an increased risk of developing chronic nephropathy as compared to non-users (or 5.9 and 5.8 as compared to hospital controls and visitor controls respectively).

**Subclinical Renal Dysfunction**

Although most of the literature on renal dysfunction due to NSAIDs pertains to clinically evident acute or chronic renal failure, there have been a few reports describing subclinical renal dysfunction in the form of functional abnormalities. The mechanisms postulated include prostaglandin mediated reversible changes in renal function and subclinical interstitial nephritis. These however, have not been proved by biopsy studies.

Various biochemical parameters have been used to evaluate...
subclinical dysfunction. Unsworth et al64 studied 11 patients admitted to the rheumatology ward for non renal causes. They had received NSAIDs for at least 6 months. NSAIDs were discontinued in all. S. urea and creatinine were measured prior to stopping NSAIDs and again reassessed before discharge or reintroduction of NSAIDs. Mean interval between admission and either discharge or reintroduction of NSAIDs was 19.4 days. There was a significant fall in the initial creatinine values on withdrawal of NSAIDs and a rise in creatinine clearance when not receiving NSAIDs, suggesting asymptomatic (reversible) renal dysfunction due to NSAIDs.

Richards et al65 studied 24 hour urine protein, creatinine clearance and N-acetyl glucose aminidase in 167 patients with RA on NSAIDs selected randomly over a 6 week period. They found no co-relation between creatinine clearance and disease duration and a weak co-relation between measured and calculated creatinine clearance. They concluded that long term use of NSAIDs was associated with few renal problems. Minor reduction in GFR was common and not related to disease duration or length of NSAID therapy. The mean duration of disease was 12 years suggesting that the rate of decline in renal function if any was not unduly rapid.

Calvo Alen et al66 studied renal function in 104 patients who had been on NSAIDs for at least 2 years. Urine analysis, serum electrolytes, serum and urinary creatinine and serum and urine osmolality were assessed. Creatinine clearance and osmolar clearance were calculated. They observed reduced concentration ability as judged by a lower specific gravity, reduced urine osmolality, a reduced osmolar clearance and increased free water clearance. These observations support the concept that chronic NSAIDs treatment causes renal damage that is consistent with subclinical interstitial nephropathy.

Reversible mild rise in creatinine has been described. Koseki et al67 studied 235 early RA patients, on NSAIDs. A rise in creatinine was found in 14 patients (6%). This was attributed to inhibition of prostaglandin synthesis due to NSAIDs in 3 cases. S. creatinine improved on stopping the drug in all the 3 cases. The rise in creatinine in the other cases was related to D-penicillamine, ACE inhibitors, diuretics, dehydration and renal hypoplasia.

Caspi et al68 studied the effect of mini-dose aspirin (75mg/day) on renal function and uric acid handling in 49 elderly patients (age 61-94). They found that creatinine and uric acid clearance rates paralleled each other during aspirin treatment. However, 1 week after aspirin discontinuation, creatinine clearance remained decreased while uric acid clearance returned to baseline suggesting that some amount of renal dysfunction persists even though creatinine returns to normal. Similar findings were noted by us.69 Of the 99 patients on long-term NSAID (> 2 years) studied, 27 showed a rise in creatinine. When mean creatinine levels at baseline were compared with mean creatinine levels on recovery (after NSAID discontinuation), a statistically significant difference in creatinine levels was noted, the level of post recovery serum creatinine being higher.

**DIFFERENTIAL RENAL SAFETY OF NSAIDS**

All groups of NSAIDs are nephrotoxic. The role of half-lives as a basis for nephrotoxicity has been studied.

Adams et al70 proposed that NSAIDs with longer half-lives are more likely to cause nephrotoxicity because of sustained prostaglandin inhibition leading to a sustained reduction in renal blood flow, whereas with short acting NSAIDs, the kidney may be better able to recover between doses. Whelton et al (1990)71 however found that agents with short half-lives, such as ibuprofen, reach steady state sooner than those with longer half-lives and hence may produce renal decompensation in a matter of days. In a cross sectional study involving 802 patients undergoing joint replacement surgery for osteoarthritis, Sturmer et al (2001)72, looked at half-life of NSAIDs as a predictor of renal dysfunction. NSAID use per se was only marginally associated with impaired renal function (odds ratio 1.4). This was almost exclusively associated with NSAIDs with a 1/2 of 4 hours or more.

The search for a kidney sparing NSAID resulted in the development of prodrugs drugs like sulindac and nabumetone. Sulindac, requires hepatic conversion from sulindac sulphone to the active sulphide moiety.73 It is less likely to inhibit renal prostaglandin synthesis since the kidney is able to reconvert the active sulphide back to the inactive sulphone molecule. However, Whelton et al, found that sulindac is not completely renal sparing.74 Mistry et al75 looked at the effect of sulindac on renal function and prostaglandin synthesis in patients with moderate chronic renal insufficiency. Short term use of sulindac in therapeutic doses did not appear to influence the excretion of prostaglandins and produced only a minor reversible change in renal function. It seems, used cautiously, sulindac may have an advantage over other NSAIDs in patients with moderate chronic renal insufficiency.

Nabumetone requires hepatic conversion to the active metabolite76. It has been shown to be associated with an insignificant change in the urinary excretion of 6-keto-PGF1α and PGE2 and little effect on serum creatinine and creatinine clearance.77

Cook et al78 compared renal effects of one months therapy with ibuprofen, sulindac and nabumetone. Though overall no statistically significant differences were found amongst these NSAIDs, 4 patients on ibuprofen and one patient on sulindac developed clinically significant decrease in renal function. They concluded that there are differences in the effects on renal function amongst NSAIDs. It was related to changes in the haemodynamic control of glomerular filtration. Nabumetone has been reported to cause tubular damage with minimal glomerular changes, presenting as progressive oedema.79

Improved renal safety was envisaged with the development of COX-2 specific inhibitors like celecoxib and rofecoxib. However, COX-2 is constitutively expressed in renal tissues of all species and may be involved in prostaglandin-dependent renal homeostatic processes and selective inhibition of COX-2 might be expected to produce effects on renal function
similar to nonselective NSAIDs.77

Whelton et al84 carried out a post hoc analysis of renal safety of celecoxib using data from 50 clinical studies involving more than 13,000 subjects. Over 5000 subjects had received celecoxib for 2 years. The incidence of renal adverse events after celecoxib was greater than that after placebo but similar to that of other NSAIDs, the most common events being peripheral oedema (2.1%), hypertension (0.8%) including exacerbation of pre-existing hypertension.

Ahmad et al79 carried out Medline search to identify published cases of ARF associated with celecoxib and rofecoxib using the US FDA adverse event reporting system. 122 and 142 domestic cases of celecoxib and rofecoxib associated renal failure respectively were identified. 19 cases were of acute renal impairment. An additional 50 reports of renal failure with these drugs were identified from drug regulatory authorities in UK, Canada and Australia. The authors concluded that the renal effects of these drugs were similar to conventional NSAIDs. They did not recommend use of these drugs in patients with advanced renal disease. Similar views were echoed in the recently published review by Brater.80 Schwartz et al75 compared the renal effects of celecoxib and rofecoxib with naproxen and placebo in healthy elderly subjects on a sodium-replete diet and found no differences between the two groups as measured by urinary sodium excretion, systolic and diastolic blood pressure, creatinine clearance or weight gain.

ARF with high doses of celecoxib has been reported.52 Alkhuja et al58 reported a case of non-oliguric renal failure in a case of rheumatoid arthritis on celecoxib within 14 days of starting therapy. Although the kidney function had improved within 30 days after presentation, it had not returned to normal.

Interstitial nephritis has been reported with celecoxib.44 Alper et al85 reported a case of interstitial nephritis associated with nephrotic syndrome in a diabetic patient who had been on celecoxib for one year for degenerative joint disease. The patient had normal creatinine level with no microalbuminuria 7 months prior to presentation. Henao et al86 reported a biopsy proven case of interstitial nephritis in an elderly diabetic patient on celecoxib for more than a year. The patient presented with subnephrotic proteinuria and ARF that required dialysis. Renal function recovered after 2 weeks of cessation of celecoxib.

Zhao et al87 used WHO/ Uppsala monitoring center safety database to compare the renal related adverse reactions with rofecoxib and celecoxib. The adverse renal impact of rofecoxib was found to be significantly greater than that of celecoxib or the traditional NSAIDs with a higher incidence of dehydration, abnormal renal function, renal failure, cardiac failure and hypertension. Whelton et al84, have reported a lesser incidence of oedema and destabilization of blood pressure control with celecoxib as compared to rofecoxib in randomized controlled trials in elderly hypertensive osteoarthritic patients. Rofecoxib has been reported to be associated with acute tubulo-interstitial nephritis.88 Morales et al86 reported a case of acute renal failure in an elderly patient after receiving a 50mg dose of rofecoxib.

It is clear that NSAIDs are associated with all forms of renal failure. While acute syndromes generally carry a good prognosis, the same is not true of CRF. Subclinical CRF can be silent forerunner of CRF.

REFERENCES


