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Cyclo-Oxygenase-2 Inhibitors and the Kidney

A Case for Caution

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Contents

Abstract

Cyclo-oxygenase (COX) is one of the key enzymes in the biosynthesis of prostaglandins. Two isoforms of this enzyme COX-1 and COX-2 are known to exist. Among other functions, prostaglandins play an important role in the protection of the gastric mucosa and maintenance of renal function in pathophysiological conditions which would otherwise threaten it. Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) block prostaglandin synthesis, resulting in gastric mucosal injury and renal dysfunction in susceptible individuals. The recent introduction of selective COX-2 inhibitors, celecoxib and rofecoxib, appear to induce less gastrointestinal morbidity. Although conclusive data are still lacking, there is evidence to suggest that COX-2 antagonists may be capable of causing some of the same renal syndromes seen in association with the older, less selective NSAIDs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have become the standard of care in conditions such as rheumatoid arthritis, osteoarthritis, and as a mainstay in the treatment of musculoskeletal pain. In fact, utilisation studies revealed that in 1983 alone, physicians in the US wrote 19.8 million prescriptions for ibuprofen.[1] During this time NSAIDs represented 4% of the entire prescription market with 473 600kg purchased by pharmacies.[1] At about the same time NSAIDs previously requiring prescriptions became available over-the-counter. In 1999 it was estimated that as many as 30 billion over-the-counter NSAID tablets were sold in the US annually, with regular use by 13 million people with arthridides.[2] However, with such widespread use come widespread adverse

effects and complications. The clinical spectrum of gastrointestinal injury includes ulcer, haemorrhage, and perforation. In 1997, 16 500 patients with rheumatoid arthritis and osteoarthritis died from gastrointestinal complications related to NSAID use.[2] The mortality rate of patients hospitalised with upper GI bleeding induced by NSAIDs ranged from 5 to 10%.[2] The financial costs of NSAID-related complications in the US were estimated to be US3.9 billion in 1982.[3]

NSAIDs are a class of anti-inflammatory agents that block the production of prostaglandins, a group of compounds that primarily exert their biological activity at the site of synthesis. Prostaglandins are unsaturated fatty acid compounds derived from the oxygenation of arachidonic acid by the cyclo-oxygenase (COX) enzyme system. NSAIDs exert their effect by inhibiting COX enzyme activity.[4,5] The kidney is active in the production and metabolism of prostaglandins.[4-6] The most abundant prostaglandin found in the renal tubules is prostaglandin-E_2 (PGE_2), which regulates sodium and chloride transport in the loop of Henle. PGE_2 also modulates water transport and renal medullary blood flow. PGI_2 is the most abundant prostaglandin in the renal cortex, and regulates renal vascular tone, glomerular filtration rate (GFR) and renin release (figure 1).[5,6]

NSAIDs are associated with a variety of renal syndromes including acute vasomotor renal failure, chronic renal failure, the nephrotic syndrome, hyperkalaemia, and hyponatraemia (table I).[4-6] PGE_2 dilates the renal vascular bed. In animal studies, inhibition of its synthesis has a profound negative effect on renal blood flow and GFR, when superimposed on a previous haemodynamic insult.[5] Inhibition of prostaglandin synthesis leads to renal decompensation in situations where renal and systemic haemodynamics are dependent on the availability of prostaglandins.[5,6] It is important to note that NSAIDs have little effect on the GFR in intact animals or human beings. Such prostaglandin dependence has been demonstrated in animal models of hypotensive haemorrhage, sodium depletion, general anaesthesia, and biliary cirrhosis.[4] In humans, acute renal failure in the setting of NSAID administration occurs commonly in situations where the kidney is more dependent on

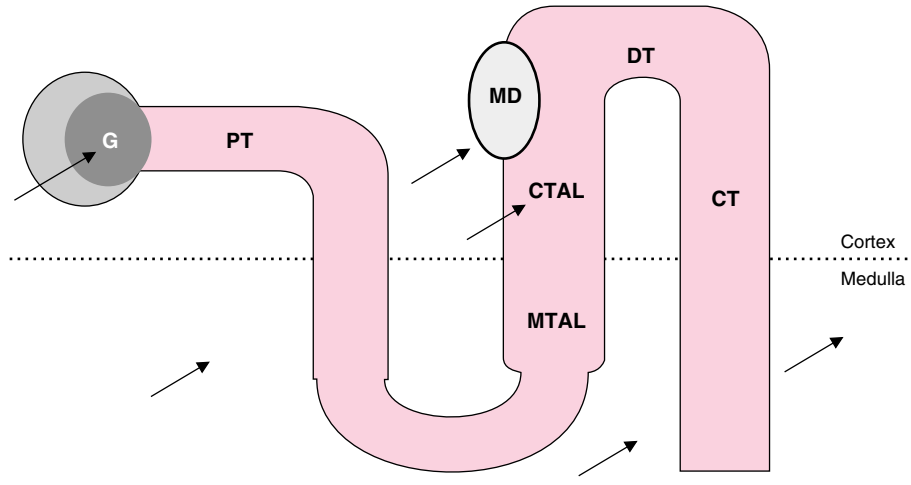

Fig. 1. Location of cyclo-oxygenase-2 activity within the mammalian kidney. **CT** = collecting tubule; **CTAL** = cortical thick ascending limb of loop of Henle; **DT** = distal convoluted tubule; **G** = glomerulus; **MD** = macula densa; **MTAL** = medullary thick ascending limb of loop of Henle; **PT** = proximal convoluted tubule.

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Table I. Clinical renal syndromes described in association with NSAIDs

Syndrome	Conventional NSAIDs	COX-2 antagonists
Acute renal failure	✓	✓
Hyperkalaemia	✓	
Hyponatraemia	✓	
Nephrotic syndrome	✓	
Fluid retention	✓	✓
Exacerbation of hypertension	✓	✓

COX-2 = cyclo-oxygenase-2; **NSAIDs** = nonsteroidal anti-inflammatory drugs.

prostaglandins in the maintenance of renal blood flow and GFR.[6] Conditions associated with a decreased circulating volume (high renin states) such as congestive heart failure, nephrotic syndrome, cirrhosis and salt depletion, place a patient at risk of developing renal failure.[4]

NSAID use is also associated with fluid and electrolyte disturbances. Prostaglandins are, for the most part, natriuretic substances.[5] The inhibition of PGE_2 impairs both natriuresis and free water diuresis in states of decreased effective circulating volume.[6] Indomethacin, for example, blunts the natriuretic effect of furosemide (frusemide). NSAIDs increase the renal tubular absorption of sodium and water.[4,6] As a result, oedema, hyponatraemia, and worsening hypertension can develop. NSAIDs impair potassium excretion by decreasing plasma renin activity and consequently aldosterone production.[4] Decreased delivery of sodium to the distal tubule contributes to the impairment of potassium excretion.[4,6] Hyperkalaemia can occur in indomethacin treated patients with normal renal function.[7]

In addition to electrolyte abnormalities, an increased risk of chronic renal insufficiency in patients treated with NSAIDs has also been reported in the literature.[8] There is evidence to link NSAID use with interstitial nephritis and papillary necrosis.[9] There have been a number of reports of a syndrome of acute renal failure with proteinuria in the nephrotic range (>3g/24h) associated with treatment with fenoprofen, indomethacin, naproxen, and tolmetin.[9] Pathological findings in this syndrome include lymphocytic infiltration of the proximal and distal renal tubules as well as fusion of the epithelial foot processes.[4,9]

1. Cyclo-Oxygenase-2 (COX-2) and its Inhibitors

Given the adverse renal and gastrointestinal adverse effects of first generation NSAIDs, researchers have directed attention to substances that can alter inflammatory cascades while inducing fewer alterations in vascular and epithelial function. The 1990s saw the recognition of two distinct isoforms of COX. These isoforms, named COX-1 and COX-2, differ in their expression, although the two share 60% amino acid homology.[10] Both enzymes are products of unique, single-copy genes located on different chromosomes: COX-1 and COX-2 are on chromosomes 9 and 1, respectively.[10]

COX-1 is the only isoform expressed in platelets, and is responsible for the production of prostaglandins that maintain the integrity of the gastric mucosa. COX-1 is mainly constitutively expressed in all tissues and is considered to be a 'housekeeping' enzyme.[11] In contrast, COX-2 is a highly regulated gene product and, with few exceptions, its expression is restricted under basal conditions. The promoter of the COX-2 gene contains a transcription factor that is sensitive to inflammatory mediators.[11] The expression of the COX-2 isoform, readily induced by interleukin-1 (IL-1), increases. in response to inflammatory stimuli and tissue damage including inflammatory arthritis.[11] COX-2 features prominently in the pathogenesis of the febrile response, pain, and tissue repair.[10,11] The activity of COX-2, and not COX-1, is stimulated by the pyrogen lipopolysaccharide.[12] Glucocorticoid hormones suppress COX-2 gene expression in cultured mesangial and tubular epithelial cells.[13] Conversely, adrenalectomy appears to induce COX-2 gene expression.[14] These observations support a pro-inflammatory role for

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COX-2 products. However, COX-2 is constitutively expressed in brain and kidney tissue.[9,15] The development of various epithelial cancers including colon and breast may involve the upregulation of COX-2 expression.[11]

Conventional NSAIDs inhibit both COX isoforms. Predictably, the recognition of two distinct isoforms, prompted an aggressive initiative to develop compounds that specifically block the COX-2 enzyme. Two commercially available medications in this category are celecoxib and rofecoxib. Their anti-inflammatory properties have been convincingly demonstrated in animal models of inflammatory arthritis.[11] Clinical experience with both celecoxib and rofecoxib reveals that their analgesic efficacy is equal to that of nonselective NSAIDs in dental pain as well as osteoarthritis.[11] Based on the experience with conventional NSAIDs, it is appropriate to ask two questions. First, what is the role of the COX-2 enzyme in the kidney? Secondly, do COX-2 inhibitors have the same renal toxicity as the first generation NSAIDs?

2. COX-2 and the Kidney: the Experimental Evidence

2.1 COX-2 and Nephrogenesis

The developing kidney expresses both COX isoforms.[16] In the postnatal rat kidney, COX-2 expression which is low at birth increases in the first 2 weeks, and gradually declines to low levels.[16] Ablation of the COX-2 gene results in cystic renal dysplasia and early death in adult mice.[17] In the postnatal period, COX-2 knockout mice have thinning of the renal cortex with crowded small subcapsular glomeruli.[17] Tubular abnormalities are also seen, including atrophy, tubular dropout, and cyst formation. Maternal administration of a COX-2 inhibitor in mice and rats may lead to similar renal pathology.[16,17]

2.2 Effects of COX-2 Inhibition on Renal Function and Blood Pressure

Data derived from studies in rodents have attempted to define the role of the COX-2 isoform in renal sodium handling. This is less straightforward than it would seem; there appear to be intrarenal regional differences in the response of COX-2 to variations in sodium balance and intraspecies differences in localisation of renal COX-2.[18]

Immunochemical and *in situ* hybridisation studies have localised cortical COX-2 expression to the macula densa and to the epithelial cells of the cortical thick ascending limb of the loop of Henle.[19,20] The macula densa regulates renin release by sensing changes in delivery of chloride to the distal tubule. In the renal medulla, COX-2 is expressed in interstitial and inner collecting duct cells.[16] In states of volume depletion, renin secretion is increased.[16]

Rats chronically deprived of sodium demonstrate increased activity of COX-2 in the region of the macula densa, suggesting a role for this enzyme in the renin-angiotensin system and sodium homeostasis.[19,20] Consistent with this hypothesis is the prominent expression of COX-2 in the macula densa.[19] COX-1 isoforms are not detected in the macula densa.[19] NS398, an experimental selective COX-2 inhibitor, reduced renin content and renin mRNA expression within the kidneys of salt depleted mice by 60%. Of note, NS398 had no effect on renal renin content in mice on a normal sodium diet.[21] Similar results have been obtained in rats subjected to sodium deprivation. In these animals, decreases in plasma renin activity were not accompanied by changes in renal or systemic haemodynamics.[22] COX-2 knockout rats fail to increase renal renin mRNA expression in response to ACE inhibition, which normally increases renin.[23] COX-2 inhibition may decrease renin production and release in experimental aortic coarctation models of renovascular hypertension.[24] In salt depleted dogs, selective COX-2 inhibition increased arterial pressure and decreased renal blood

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flow as well as urine flow rate compared with dogs on a normal salt diet.[25]

These data suggest a compensatory role for COX-2–derived eicosanoids in response to conditions that normally incur systemic and renal haemodynamic consequences. The consequences of COX-2 inhibition have been examined in rats with heart failure on the basis of aortocaval fistula. In this model, renal expression of both renal COX-1 and COX-2 is up-regulated in proportion to the severity of the disease. This adaptation occurs primarily in the renal medulla.[26] In lupus nephritis, renal function depends on vasodilatory prostaglandins, and inhibition of COX via conventional NSAIDs lowers GFR.[27] Investigations show that COX-2 specific staining in kidney specimens is stronger from patients with active lupus nephritis, especially in the glomerulus.[27] These observations suggest that COX-2 functions in a compensatory fashion in the respective settings of reduced effective circulatory volume and intrinsic renal disease. However, not all evidence is consistent with this hypothesis. SC-236, another selective COX-2 inhibitor did not reduce GFR in rats with ascites.[28] Further, inhibition of COX-2 may not blunt the naturiuretic response to increased renal hydrostatic pressure caused by volume expansion.[29] Thus, the exact importance of COX-2 activity remains somewhat unclear.

Conventional NSAIDs such as meclofenamate have been used to reduce proteinuria in clinical nephrotic syndrome.[30] Fluoside, a selective COX-2 inhibitor, has an antiproteinuric drug effect in rats with Heymann nephritis.[30] Heymann nephritis is a model of experimentally induced glomerulonephritis that is also associated with increased COX-2 protein expression.[30] Investigators have provided a rationale for using inhibitors of COX-2 in various forms of renal disease. Prostaglandin production is increased in glomeruli of rats that have undergone subtotal nephrectomy, a model of chronic progressive renal disease.[31] This increase appears to be mediated by the COX-2 system.[32] In this renal ablation model, rats develop proteinuria and hypertension; it is proposed that COX-2 inhibitors may retard such progression.[32] The use of COX-2 inhibitors for renoprotection must be approached cautiously. The above-normal activity of COX-2 in glomeruli of chronically diseased kidneys bespeaks a compensatory role, perhaps in the compensatory maximisation of GFR. While inhibition of the enzyme may alleviate proteinuria, this effect may come at the expense of reduced excretory capacity. In diabetic rats, COX-2 inhibition lowers GFR.[33]

3. Effects of COX-2 Inhibition on Renal Function and Blood Pressure: Clinical Observations to Date

Only a few clinical studies have examined the direct effects of celecoxib or rofecoxib on renal function, sodium and potassium balance, or blood pressure. Some of the clinical trials that focus on gastrointestinal outcomes have included data pertaining to kidney function.

Several studies have examined the effect of COX-2 inhibitors on renal function in humans with salt depletion. Salt depletion is a hypovolemic, hyperreninemic state placing the patient at risk of acute renal failure. In a randomised, controlled trial,[34] the effect of single or multiple doses of indomethacin 75 mg/day, rofecoxib 12.5 or 25 mg/day or placebo on GFR, creatinine clearance, and urinary electrolytes was measured over 24 hours in 75 elderly patients with sodium depletion and normal renal function at baseline. Compared with placebo, single doses of rofecoxib and indomethacin decreased peak GFR by 0.23 ml/sec and 0.18 ml/sec, respectively.[34] There were no significant differences in GFR between the two drugs. Both rofecoxib and indomethacin increased serum potassium concentrations. In the single dose arm of the study, rofecoxib reduced potassium excretion compared with placebo. Indomethacin also reduced potassium excretion compared with placebo. In the multiple dose arm, neither drug caused consistent changes in peak reduction of urinary sodium or potassium excretion. Only rofecoxib caused a sig-

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nificant decrease in GFR as determined by iothalamate clearance. These findings suggest that COX-2 inhibitors do not offer any advantage in terms of renal function.[34]

In a similar study by Rossat et al.[35] younger adults, with normal renal function and sodium depletion, were randomised to receive celecoxib 200 or 400mg twice daily, naproxen 500mg twice daily, or placebo for 7 days. While naproxen and celecoxib had no effect on blood pressure or heart rate, both drugs decreased sodium and water excretion. A transient decrease in GFR occurred with the higher dose of celecoxib during the first day of the study.[35]

One additional randomised controlled trial by Whelton et al.[36] compared celecoxib 200mg twice daily for 5 days and subsequently 400mg twice daily with naproxen 500mg twice daily for 10 days in healthy elderly patients with no salt restriction. Naproxen had a tendency to reduce GFR to a greater degree than celecoxib. Again, both agents reduced sodium excretion. There was no mention of incidences of acute renal failure in any of the three clinical trials mentioned above.[34-36] One open-label trial examined the use of meloxicam, a COX-2 inhibitor, in 25 patients with pre-existing renal impairment. Estimated creatinine clearance did not change significantly from baseline over 3 week study period.[37] There were also no elevations in serum potassium or urea levels.[37]

In a placebo-controlled study, Catella-Lawson and co-workers[38] compared the renal effects of the specific COX-2 inhibitor MK-0966 with those of the nonselective COX inhibitor indomethacin. The study participants were healthy adults aged 59 to 80 years. Both indomethacin and MK0966 lowered urinary sodium excretion significantly, and to a comparable extent. GFR fell only in the indomethacin-treated group. The authors concluded that COX-1 plays a greater role in GFR maintenance, and COX-2 in sodium homeostasis.[38]

The Celecoxib Long-term Arthritis Safety Study (CLASS) investigated gastrointestinal morbidity with celecoxib compared with ibuprofen or diclofenac in 7968 patients. [39] The investigators included in their report data on renal and cardiovascular effects. The overall incidences of elevated blood urea nitrogen, creatinine, and blood pressure, relative to baseline, were significantly greater in patients who received nonselective NSAIDs. The overall incidences of myocardial infarction and congestive heart failure were similar in both arms.[39]

A *post hoc* analysis of the celecoxib clinical trial programme reviewed data from 50 studies on the adverse events reported in arthritis trials.[40] In reviewing reported adverse events, celecoxib and NSAIDs had similar incidences of renal effects including oedema, hypertension, and acute renal failure. However, this retrospective analysis is somewhat limited because of differences in study design and limited description of methods of data analysis.

Two case reports of COX-2 inhibitors causing acute renal failure in patients with pre-existing kidney disease and congestive heart failure have been published.[41] In the first case, a 63-year-old man with left-ventricular hypertrophy, a creatinine level of 2.8 mg/dl, and coronary artery disease developed acute renal failure and volume overload while receiving treatment with celecoxib. He received a dose of 200mg twice daily for arthritic pain for 16 days and developed oedema with an increase of serum creatinine to 4.9 mg/dl. His renal function returned to baseline after discontinuation of celecoxib.[41] In the second case report, a 68-year-old man with a history of cardiomyopathy, hypertension and diabetic nephropathy with a baseline creatinine of 3.5 mg/dl developed oedema and worsening renal function after 13 days of treatment with celecoxib 200mg twice daily for 13 days. Renal function in this case also returned to baseline after discontinuation of celecoxib.[41] Renal function returned to baseline after discontinuation of celecoxib and administration of furosemide.

The logical question posed by the above data is whether COX-2 inhibitors are safe for use in patients with established renal disease, congestive

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heart failure, or liver disease. The increased expression of COX-2 enzymes in animals with salt depletion implies that inhibition of the enzyme would be detrimental to renal perfusion and renal function in conditions of congestive heart failure and nephrotic syndrome. To date, the controlled trials investigating renal function as a primary outcome suggest that NSAIDs and COX-2 inhibitors do not greatly differ in the reduction of GFR or urinary sodium excretion. Clearly, further studies are necessary. However, performing controlled clinical trials examining the safety of COX-2 inhibitors in patients at risk poses several obvious difficulties.

4. Conclusion

The recent CLASS study compared the incidences of upper gastrointestinal ulcers and ulcer complications between conventional NSAIDs and celecoxib. Fewer celecoxib-treated patients developed symptomatic ulcers and subsequent complications.[11] CLASS provided optimism that COX-2 inhibitors have an improved gastrointestinal safety profile compared with traditional NSAIDs. It is logical to conclude that the use of COX-2 inhibitors will increase in the coming years. Will their widespread use lead to an epidemic of renal and electrolyte disorders?

The report by Perrazella and Eras[41] of an association between COX-2 inhibition and acute renal failure, in two patients with underlying renal and cardiac disease, provides a rationale for some concern. In both cases, renal function returned to baseline after discontinuation of celecoxib. The exact magnitude of the risk for NSAID-related renal and electrolyte disorders is unknown. Cases are no longer reported with the same frequency as in the decade of the 1980s. While anecdotal accounts periodically appear of adverse renal effects associated with COX-2 antagonists, the database is still scant. Pending further clinical information, close monitoring, or even avoidance of COX-2 inhibitors in patients with underlying renal failure, cardiac failure, or cirrhosis would seem the safest clinical approach (figure 2).

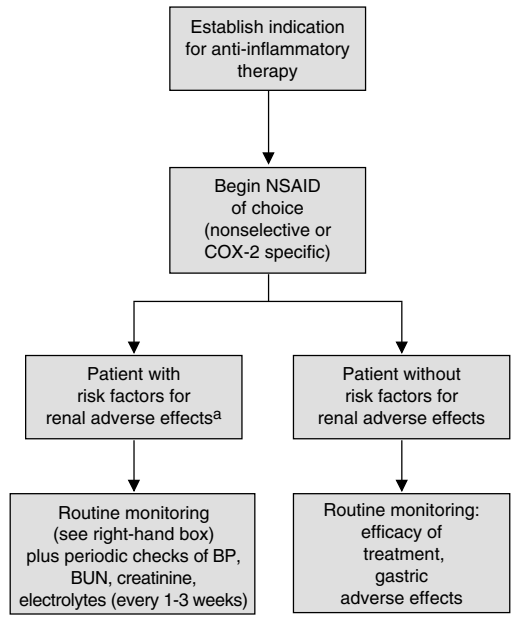

Fig. 2. Suggested algorithm for prescribing cyclo-oxygenase inhibitors. **BP** = blood pressure; **BUN** = blood urea nitrogen; **COX-2** = cyclo-oxygenase-2; **NSAID** = nonsteroidal anti-inflammatory drug. a Risk factors include age >70 years, hypertension, diabetes mellitus, cirrhosis, congestive heart failure, history of renal disease or electrolyte imbalance.

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