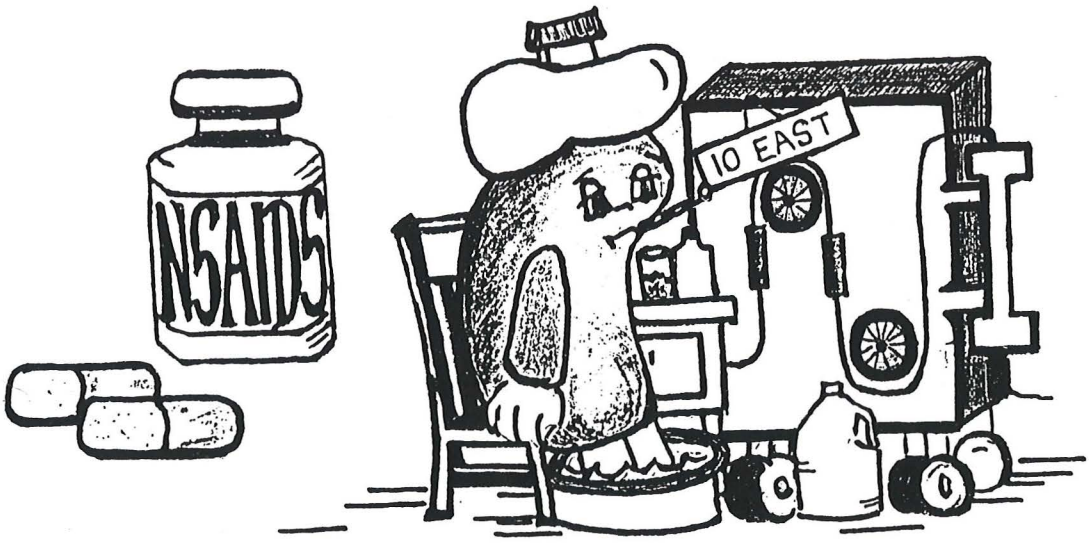
Pain vs Renal Failure:
An Over the Counter Choice

Renal Syndromes Associated with Use of Non-steroidal Anti-inflammatory Drugs



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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are some of the most widely utilized therapeutic agents used in clinical practice today (1,2). Conservative estimates state that approximately 40-50 million people annually are exposed to these agents. When classified according to generic class, NSAIDs are the most commonly prescribed drugs in the United States. The widespread use of these agents support the notion that NSAIDs are effective drugs in the treatment of the many clinical conditions for which they are prescribed. At the same time, however, these figures indicate that the number of patients at risk for adverse events related to the use of these agents is rapidly expanding. This concern is further heightened by the availability of ibuprofen and, most recently, naprosyn on an over-the-counter basis.

While the gastrointestinal toxicity of these medications is well known, it has become increasingly apparent that the kidney is also an important target for untoward clinical events. In fact, the renal toxicity associated with the use of NSAIDs can be divided into one of several distinct clinical syndromes (Table 1). These include a form of vasomotor acute renal failure, nephrotic syndrome associated with interstitial nephritis, chronic renal injury, and abnormalities in sodium, water, and potassium homeostasis. The common link in these syndromes is a disruption in prostaglandin metabolism, the vary class of compounds whose synthesis is inhibited by these agents.

Table 1. Renal syndromes associated with NSAIDs

- Vasomotor acute renal failure
- Nephrotic syndrome with tubulointerstitial nephritis
- Chronic renal injury
- Salt retention
- Hyponatremia
- Hyperkalemia

Prostaglandin Biosynthesis and Compartmentalization

Prostaglandins are members of a class of compounds termed eicosonoids. Eiconsonoids are biologically active fatty acids which are all derived from the oxygenation of arachidonic acid. The particular enzyme involved in the oxygenation process dictates which class of eicosonoid will be synthesized. Oxygenation of arachidonic acid by the enzyme cyclooxygenase is responsible for prostaglandin and thromboxane synthesis (Figure 1). The enzyme lipoxygenase converts arachidonic acid to leukotrienes, lipoxins, and eventually to hydro fatty acid derivatives such as hydroxyeicosatetraenoic acid (HETE). Finally, oxygenation by cytochrome P-450 generates epoxyeicosatrienoic acids (EETS).

The availability of free arachidonic acid is the rate limiting step in eicosonoid biosynthesis. Normally, arachidonic acid is

found esterified to membrane phospholipids where it undergoes deacylation primarily under the influence of phopholipase A2. Phospholipase A2 mediated arachidonic acid release is a calcium/calmodulin-dependent step that is stimulated by vasopressin, bradykinin, angiotensin, and norepinephrine (3). Corticosteroids inhibit this reaction by inducing the formation of an inhibitor of phospholipase A2 called macrocortin or lipomodulin. Once released, free arachidonic acid is either re-esterified back into membrane lipids or is converted into one of the biologically active eicosonoids.

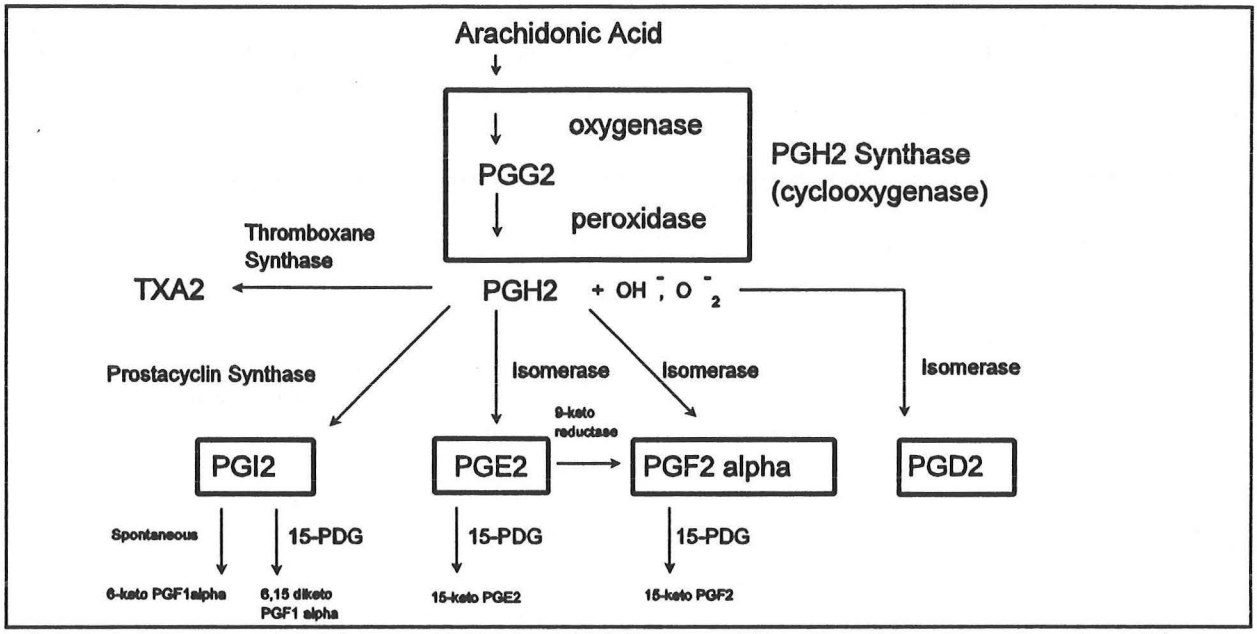


Figure 1. Synthetic and degradative pathways for prostaglandins and thromboxane.

The first step in the synthesis of prostaglandins and thromboxanes is a cyclooxygenase reaction in which arachidonic acid is converted into the cyclic endoperoxide PGG2. PGG2 then undergoes a peroxidase reaction to form a second endoperoxide called PGH2 which is accompanied by the formation of a superoxide radical. Both of these reactions are catalyzed by PGH synthase, an enzyme that is commonly referred to as cyclooxygenase (4). This enzyme exists as two isoforms (PGH1 and PGH2), both of which possess the cyclooxygenase and peroxidase activity. These two reactions occur at distinct but neighboring sites on the same enzyme (4). Once formed, PGH2 has a short half life and is rapidly acted upon by a series of enzymes that produces biologically active prostaglandins or thromboxane. Prostacyclin synthase acts to form prostacyclin (PGI2), thromboxane synthase forms thromboxane (TXA2), and isomerases are responsible for the formation of PGE2, PGD2, and PGF2 alpha. PGE2 can be converted to PGF2 alpha by 9-keto reductase, an enzyme that is stimulated by high-salt diet and

inhibited by furosemide (5). Both aspirin and other NSAIDs exert their prostaglandin inhibitory effects by inhibiting PGH synthase. The decrease in prostaglandin synthesis as well as the decrease in superoxide radical formation contribute to the anti-inflammatory effects of these agents.

Prostaglandins are synthesized on demand and exert physiologic effects in discrete microenvironments along the nephron in close proximity to where they are synthesized (Table 2). Due to the virtual absence of distant effects, these compounds are best

Table 2. Compartmentalization and function of renal prostaglandins

Site	Eicosanoid	Action
Arterioles	PGI2, PGE2	Vasodilation
Glomeruli	PGI2>PGE2 (human) PGE2>PGI2 (rat) TXA2	Maintain GFR Vasoconstriction
Tubules	PGE2, PGF2α	Enhance NaCl and water excretion
Interstitial cells	PGE2	Enhance NaCl and water excretion, Influences regional blood flow
Juxtaglomerular apparatus	PGE2, PGI2	Stimulate renin release

regarded as autocoids rather than hormones. Variations in the synthetic and degradative machinery along the length of the nephron account for the differing types and amounts of prostaglandins found in any given segment (6). PGI2 is the most abundant prostaglandin produced in the cortex and is primarily synthesized in cortical arterioles and glomeruli (7). This location corresponds to the known effects of PGI2 to importantly regulate renal vascular tone, glomerular filtration rate, and renin release. PGE2 and thromboxane A2 are also produced in the glomerulus and therefore may exert effects at this site. The most abundant prostaglandin found in the tubules is PGE2 (6,7). The cortical and especially the medullary portion of the collecting duct is the dominant site of PGE2 synthesis. Lesser amount are found in the thin descending and thick ascending limb with the least amount of synthesis found in the proximal tubule. Medullary interstitial cells are also a rich source of PGE2 production. This distribution provides the anatomic basis for PGE2 to modulate sodium and chloride transport in the loop of Henle, arginine vasopressin mediated water transport, and vasa recta blood flow. PGF2 alpha is synthesized primarily by medullary interstitial cells and less by the papillary

collecting tubule and glomeruli. Prostaglandin-degradative enzymes are found in both the cortex and medulla but are most abundant in the cortex. Except for PGI2 which undergoes spontaneous hydrolysis to 6-keto-PGF1 alpha, prostaglandins are rapidly metabolized into inactive products by a 15-prostaglandin dehydrogenase (8). Increased concentration of this enzyme in the proximal nephron may facilitate degradation of prostaglandins delivered to the proximal tubule by glomerular filtration (9).

Biologic Actions of Prostaglandins in the Kidney

Under baseline euvolemic conditions prostaglandin synthesis is negligible and as a result these compounds play little to no role in the minute to minute maintenance of renal function. Where these compounds come to serve a major role is in the setting of a systemic or intrarenal circulatory disturbance. This interaction is best illustrated when examining renal function under conditions of volume depletion (Figure 2). In this setting, renal blood flow is decreased while sodium reabsorption, renin release, and urinary concentrating ability are increased. To a large extent, these findings are mediated by the effects of increased circulating levels of angiotensin II (AII), arginine vasopressin (AVP), and catechols. At the same time, these hormones stimulate the

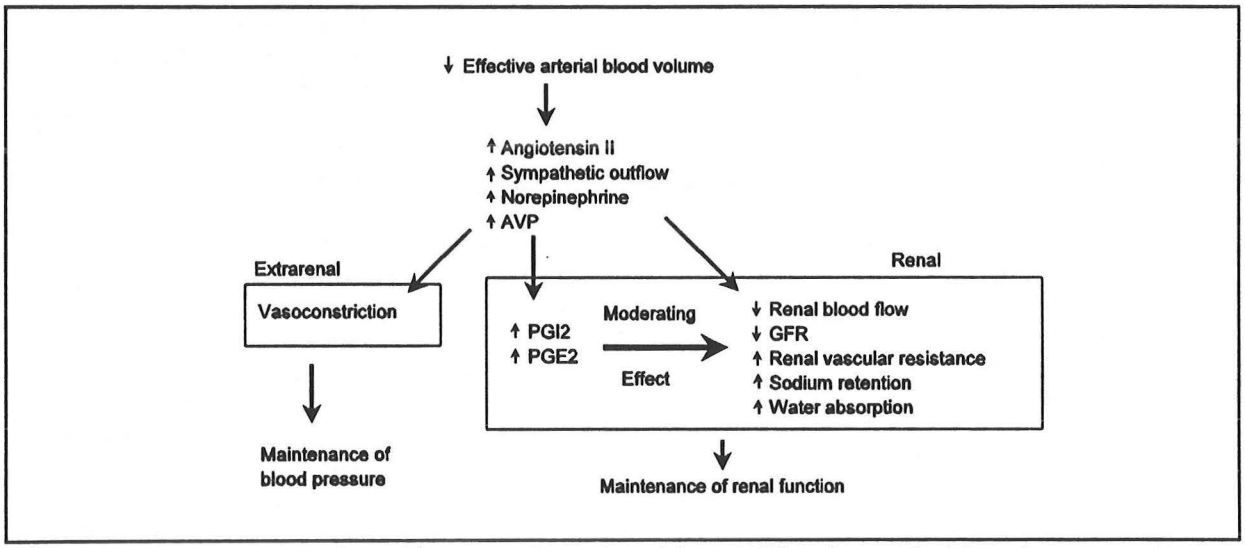


Figure 2. Prostaglandins moderate the effects of the hormonal systems that elicit their synthesis.

synthesis of renal prostaglandins which, in turn, act to dilate the renal vasculature, inhibit salt and water reabsorption, and further stimulate renin release. Prostaglandin release under these conditions serves to dampen and counterbalance the physiologic effects of the hormones that elicit their production. Predictably, inhibition of prostaglandin synthesis will lead to unopposed activity of these hormonal systems resulting in exaggerated renal

vasoconstriction and magnified antinatriuretic, antirenin, and antidiuretic effects.

Effects of Prostaglandins on Renal Vascular Tone

Prostaglandins have primarily a vasodilatory effect upon the renal vasculature (10). Intrarenal infusion of PGI2 and PGE2 or their immediate precursors, arachidonic acid and endoperoxide, has been shown to increase renal blood flow. Earlier infusion studies in the rat suggesting that PGE2 was in fact a vasoconstrictor can be explained by the simultaneous effect of PGE2 to augment renin release with subsequent formation of AII. The vasoconstrictive properties of increased intrarenal AII production would blunt the vasodilatory effect of PGE2 and thus result in a vasoconstrictive pattern. In fact, repeat of these studies in the setting of an AII receptor blocker allow for the direct vasodilatory effects of PGE2 to become fully manifest (11).

This type of interaction may explain discrepant results with regards to the vascular effects of prostaglandins recently reported in normal humans. Natov et al., found that intravenous infusion of prostacyclin (PGI2) resulted in a significant increase in renal plasma flow and decrease in renal vascular resistance without changing glomerular filtration rate (12). By contrast, oral misoprostal, a stable analogue of PGE1, was found to significantly decrease both renal plasma flow and glomerular filtration rate. Interestingly, analysis of dextran sieving curves and renal hemodynamic parameters as well as direct measurement of plasma renin activity found evidence of an activated renin-angiotensin system associated with the misoprostal infusion as compared to the prostacyclin study. In contrast to the renal effects of misoprostal noted above, Conte et. al., found that intravenous infusion of PGE1 into healthy human subjects resulted in renal vasodilation and an increase glomerular filtration rate (13). It should be noted that in this latter study, subjects were first water restricted and given 1-deamino-8-D-arginine-vasopressin to produce maximal antidiuresis, conditions which favor baseline renal vasoconstriction. As discussed below, prostaglandins are potent vasodilators in this setting. Differences in basal renal tone may explain the conflicting results noted in these later two studies (12,13). Thus, the bulk of data are consistent with a direct vasodilatory effect of the E and I series of prostaglandins. When interpreting discrepant results noted in the literature, it is important to take into account potential differences in baseline renal vascular tone as well as any stimulatory effect that prostaglandins may have on the renin-angiotensin system.

Prostaglandins play a role in the distribution of renal blood flow to different regions of the kidney. Prostaglandin stimulation results in a preferential increase in blood flow to the more juxtamedullary nephrons (14). By contrast, inhibition of prostaglandin synthesis results in a selective reduction of flow to

inner cortical nephrons while flow remains well preserved in the outer cortex (15). In addition to influencing regional blood flow, prostaglandins have been shown to have a vasoregulatory role at the level of the interlobular, afferent and efferent arterioles as well as the glomerular mesangium. In isolated renal arterioles both PGE2 and PGI2 attenuate AII- and norepinephrine-induced afferent arteriolar vasoconstriction. On the efferent side of the circulation, PGI2 similarly antagonizes AII- and norepinephrine-induced vasoconstriction but PGE2 is without effect (16). In addition to local production, vascular reactivity of the efferent arteriole appears to be influenced by prostaglandins produced in the upstream glomerulus (17). In this regard, Arima et al. found that orthograde infusion of AII (afferent arteriole-glomerulus-efferent arteriole) resulted in less vasoconstriction of the efferent arteriole as compared to when infused in a retrograde fashion (efferent arteriole-glomerulus-afferent arteriole). Pretreatment with indomethacin markedly increased the vasoconstrictive effect during orthograde infusion but was without effect during the retrograde infusion. In addition to a vasodilatory effect on the afferent and efferent arterioles, prostaglandins have been shown to attenuate mesangial cell contraction induced by AII, endothelin, AVP, and platelet activating factor (18-21)(Figure 3). Contraction of these cells will normally cause a decrease in the total glomerular capillary surface area and result in a fall in the GFR. Mesangial cell synthesis and release of PGI2 (humans) and PGE2 (rat) dampens the constrictor effects of these hormones such that the glomerular capillary surface area is maintained thereby minimizing any fall in GFR. Thus, in the setting of enhanced hormonal constrictor activity, prostaglandins play a major role in maintaining glomerular hemodynamics by exerting a vasodilatory effect at the level of the afferent and efferent arteriole as well as within the glomerular mesangium.

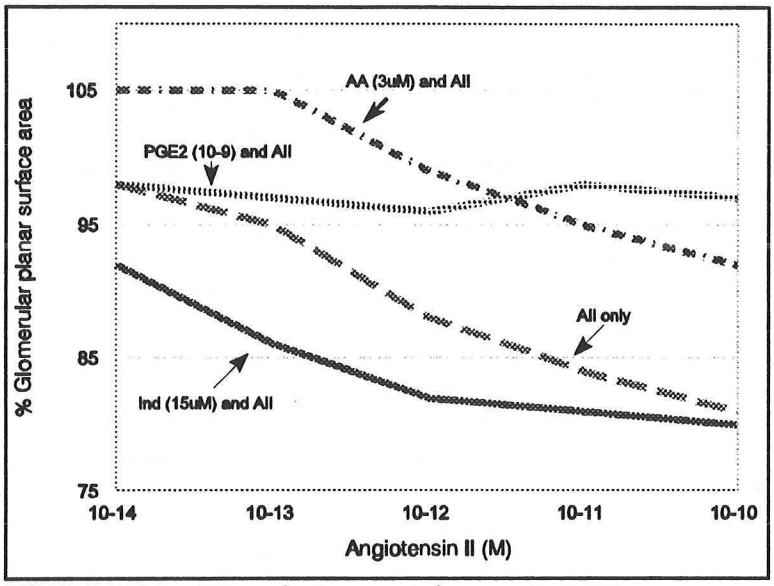


Figure 3. The interaction of AII, prostaglandins, and indomethacin on mesangial cell contraction.

NSAID-Induced Vasomotor Acute Renal Failure

Prostaglandins appear to play a negligible role in maintenance of renal function under normal circumstances. This conclusion is based on studies in both experimental animals as well as humans. In conscious, sodium replete, dogs (22-27) and rats (28-30), inhibition of renal prostaglandin synthesis with a variety of NSAIDs does not alter baseline renal blood flow or glomerular filtration rate. Similarly, renal hemodynamics are unaffected in normal humans after both short (31,32) and long term administration of aspirin (33). In related studies, administration of indomethacin to healthy volunteers was also found to produce no change in renal hemodynamics (34-38).

A sharply different effect of cyclooxygenase inhibition is observed when systemic hemodynamics are compromised. Under conditions of circulatory distress, renal blood flow represents a balance between vasoconstrictor influences on the one hand and vasodilatory prostaglandins on the other. Predictably, administration of NSAIDs in this setting will shift this balance towards unopposed vasoconstriction and potentially result in a precipitous decline in renal function.

The interplay between vasoconstrictive effectors and vasodilatory prostaglandins is particularly well illustrated in a series of studies utilizing a model of hemmorrhage in dogs (67,68) (Figure 4). In these animals subjected to hemmorrhage, prostaglandin synthesis inhibition was associated with a marked reduction in renal blood flow as compared to prostaglandin-intact dogs. This renal ischemic response was found to be partly reversed after infusion of an AII antagonist or after renal denervation. When renal denervation was combined with the AII antagonist, renal blood flow was restored to values comparable to that in the non-prostaglandin-inhibited animals. Clearly, these findings illustrate the pivotal role that prostaglandins play in opposing

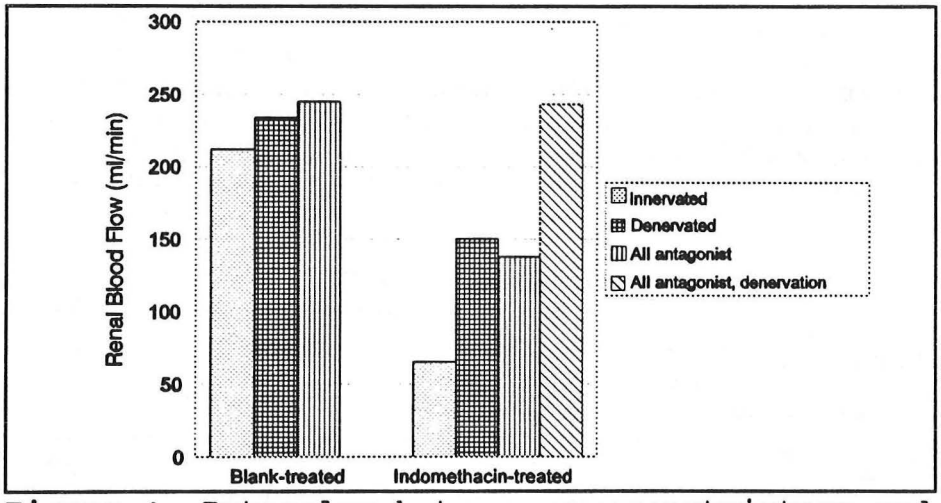


Figure 4. Interplay between vasoconstrictors and prostaglandins in dogs with hemorrhage.

the renal ischemic effects of AII and renal nerves.

The modulating effect of vasodilatory prostaglandins on renal hemodynamics can be expected to roughly parallel the extent to which vasoconstrictor effectors are activated. In turn, the activity of these effectors will reflect the degree of circulatory distress. With only mild perturbations in the circulation, one can begin to detect a discernable effect of prostaglandins on renal blood flow. For example, unlike subjects ingesting an ad lib sodium diet, normal subjects placed on a salt restricted diet will demonstrate a modest fall in creatinine clearance and renal blood flow following the administration of aspirin or indomethacin (39,40). Similar findings can be demonstrated in dogs which are first rendered salt depleted (25).

Diuretic therapy is another common clinical situation where NSAIDs may exert a deleterious effect on renal function in otherwise normal subjects (37). Like sodium restriction, diuretics increase the dependence of renal blood flow and glomerular filtration rate on vasodilatory prostaglandins and potentiate the deleterious effects of prostaglandin inhibition with cyclooxygenase inhibitors (41). The degree to which renal function is disturbed, however, appears to vary as to what diuretic-NSAID combination is used. In this regard, Favre et al., found that the combination of triamterene and indomethacin given to normal subjects resulted in a marked decline in creatinine clearance (37). By contrast, only a mild decrease in creatinine clearance was found when indomethacin was given in combination with furosemide, hydrochlorothiazide, or spironolactone. Interestingly, triamterene was the only diuretic associated with a marked increase in urinary prostaglandin secretion. Although there was little evidence to suggest that the renal failure patients were volume depleted, it would appear that triamterene by some unknown mechanism renders the renal circulation critically dependent on vasodilatory prostaglandins. As a result, triamterene in combination with a NSAID should only be used with extreme caution.

As alterations in the circulation become more pronounced rendering the renal circulation more dependent upon vasodilatory prostaglandins, cycloxygenase inhibition can be expected to result in more profound changes in renal hemodynamics (Table 3). In congestive heart failure a decrease in effective circulatory volume is the proximate cause for activation of neurohumoral vasoconstrictor forces which participate in the maintenance of systemic

Table 3. Risk factors for NSAID-induced renal failure. (↓ EABV)

- Congestive heart failure
- Cirrhosis
- Nephrosis
- Hemorrhage
- Sepsis, hypotension
- Diuretics (triamterene)
- Postoperative patients with "third space" fluid
- Volume depletion

arterial pressure and result in increased total peripheral vascular resistance. Importantly, the rise in renal vascular resistance is less than that seen in the periphery (42). Vasodilatory prostaglandins function in a counterregulatory role attenuating the fall in renal blood flow and glomerular filtration rate that would otherwise occur if vasoconstrictor forces were left unopposed (43). This delicate balance between constrictor and dilator forces is best demonstrated when inhibitors of the cyclooxygenase pathway are given. In a model of congestive heart produced by inflation of a balloon in the thoracic inferior vena cava, the interaction of prostaglandins and renal blood flow was examined. Upon inflation of the balloon, a fall in cardiac output was accompanied by a significant rise in systemic vascular resistance, plasma renin activity, and norepinephrine concentration. Renal blood flow fell slightly although renal vascular resistance did not change. Following administration of indomethacin, there was a striking decline in renal blood flow accompanied by an increase in renal vascular resistance. Similar findings were reported after administration of meclofenamate in a model of high output congestive heart failure (45). In a rat model of congestive heart failure, micropuncture studies performed after administration of indomethacin revealed an increase in efferent arteriolar resistance over values obtained in the absence of the NSAID. In addition, there were further decreases in glomerular plasma flow and single nephron glomerular filtration rate.

Increased urinary excretion of PGE2 in humans with congestive heart failure suggests that vasodilatory prostaglandins are playing a similar protective role in maintaining renal function (47,48). In fact, the urinary excretion of PGE2 parallels the degree of activation of the renin-AII system, which in turn, parallels the severity of the underlying heart failure (47). In one patient with compensated congestive heart failure, administration of indomethacin for treatment of gout resulted in acute renal failure which

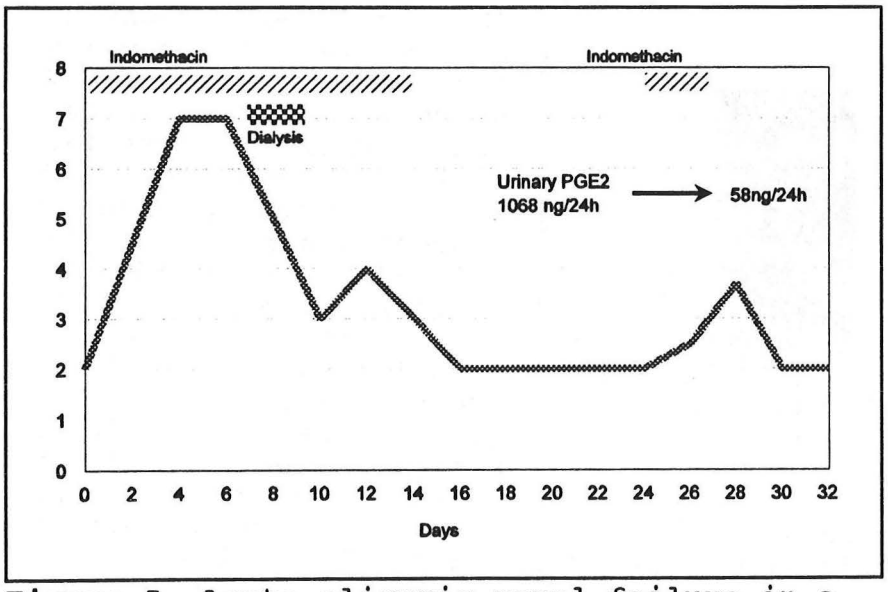


Figure 5. Acute oliguric renal failure in a 54 yo woman with compensated CHF treated with indomethacin for gout. The patient was later rechallenged with indomethacin.

resolved upon discontinuation of the drug (48)(Figure 5). Within 12 hours of being rechallenged with the same agent, the patient developed oliguria followed by weight gain, hyponatremia, and an increase in the serum creatinine concentration. All of these changes occurred in the setting of a fall in the urinary excretion of PGE2 (). In infants with a patent ductus arteriosis, NSAIDs have been used as a pharmacologic means to aid in the closure of the vessel. In those patients with congestive heart failure, this therapy is often complicated by the development of oliguria and varying degrees of acute renal failure (49).

Cirrhosis is another clinical condition in which the integrity of the renal circulation can become critically dependent upon vasodilatory renal prostaglandins. In a canine model of chronic liver disease produced by ligation of the common bile duct, urinary excretion of PGE2 and 6-keto PGF1 alpha were found to be increased (50). Following the administration of indomethacin, urinary prostaglandin excretion fell and there was a significant decline in renal blood flow and GFR. A similar protective effect of renal prostaglandins is seen in cirrhotic humans as evidenced by the occurence of renal failure following the administration of NSAIDs. As little as 25 or 50 mg of indomethacin may result in a 90% decline in the glomerular filtration rate (51-54). The renal impairement is reversible and usually resolves within 24-48 hours after cessation of the drug. Cirrhotic patients with ascites and a low urinary sodium concentration tend to be the most suceptible to develop acute decrements in renal function following the administration of NSAIDs (55)(Figure 6). These patients have a more marked decrease in effective circulatory volume which in turn leads to higher levels of circulating catechols, angiotensin II, and AVP (56,57). As a result, the renal circulation in this subset of patients is more critically dependent upon the effect of vasodilatory prostaglandins. As seen in patients with congestive heart failure, these patients have high urinary concentrations of PGE2 which

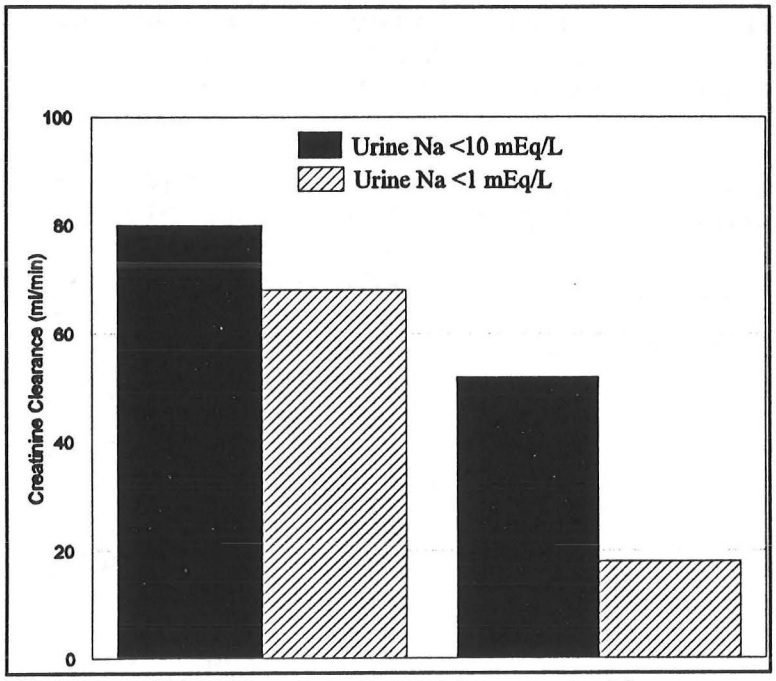


Figure 6. Effect of NSAID on CrCl as a function of urinary Na in human cirrhotics.

decline in parallel with the fall in GFR (53,55).

Renal prostaglandins may play an important role in maintenance of renal hemodynamics in nephrosis. GFR and filtration fraction are moderately decreased in most patients with the nephrotic syndrome (58,59). Micropuncture studies in an experimental model of the nephrotic syndrome have indicated that relative preservation of renal plasma flow may serve an important role in attenuating the fall in glomerular filtration rate that would otherwise occur due to a reduction in the ultrafiltration coefficient (60). In this setting, locally produced vasodilatory prostaglandins may serve to reduce afferent arteriolar resistance thereby increasing renal plasma flow and increasing filtration pressure (61,62). Administration of NSAIDs in this setting would lead to increased afferent arteriolar tone. The resulting fall in renal plasma flow and filtration pressure combined with the allready decreased ultrafiltration coefficient would result in a dramatic fall in GFR (61). Indeed, administration of prostaglandin synthesis inhibitors to nephrotic subjects is commonly associated with a fall in GFR and may precipitate acute renal failure in some patients (63-66). Other settings in which there is increased vasoconstrictive input focused on the kidney rendering it particularly vunerable to the deleterious effects of NSAIDs include endotoxic shock (69) and anesthesia (70).

Table 4. Clinical features of NSAID-induced renal failure

- Oliguria
- Usually occurs within a few days of beginning medicine
- Hyperkalemia out of proportion to renal failure
- Fractional excretion of Na low
- Usually does not require dialysis
- Usually reversible

Risk factors for the development of NSAID-induced acute renal failure are not necessarily confined to conditions characterized by decreases in absolute or effective circulatory volume (Table 5). One such example is the presence of underlying chronic renal failure. In this setting, increased vasodilatory prostaglandins are thought to play an adapative role in minimizing the decline in global renal function by increasing GFR in surviving nephrons through increased renal blood flow. The signal for increased prostaglandin production is generally not a disturbance in the systemic circulation leading to increaed circulating levels of AII and catecholamines, but rather, intrarenal mechanisms leading to generation of vasoactive compounds within the glomerular microcirculation (71). In immune mediated glomerular injury, increased production of vasodilatory prostaglandins have been shown to minimize the vasoconstrictive effects of intrarenally generated thromboxane (72-74). Similarly, prostaglandins are likely to

antagonize the effects of other vasoactive compounds such as platelet activating factor and lipoxygenase products (76,77). In models of renal insufficiency which are not immune mediated, prostaglandins also appear to play a protective role in the maintenance of renal hemodynamics (78,79). Following surgical ablation of renal mass in rats, there is a sustained increase in the glomerular formation of PGE2. After the the admnistration of indomethacin, these animals exhibit a significant decline in GFR (78,79). In this setting, intrarenal production of AII may be the proximate cause of increased prostaglandin synthesis.

Table 5. Risk factors for NSAID-induced ARF. (Nl or ↑ EABV)

- Pre-existing chronic renal failure
- Glomerulonephritis
- Elderly
- Contrast-induced nephropathy
- Obstructive uropathy
- Cyclosporine A

Studies in humans also suggest an important role for prostaglandins in preserving renal hemodynamics in the setting of chronic renal insufficiency (80). Initial observations in patients with systemic lupus erythematosis found that administration of therapeutic doses of aspirn was associated with striking reductions in renal function (81). A more detailed study in seven female patients with systemic lupus erythematosis treated with aspirn found that the decline in renal function was preceeded by a fall in baseline elevated urinary PGE2 levels and in this manner were similar to patients with cirrhosis and congestive heart failure who demonstrated falls in renal function following the use of indomethacin (82). A fall in GFR in association with a decline in urinary PGE2 has also been seen with other NSAIDs (83). Histologic studies in lupus patients who develop acute renal failure in association with the use of NSAIDs typically show changes of acute tubular necrosis superimposed on the underlying glomerular disease (84,85).

A correlation between the urinary excretion of PGE2 and NSAID-induced renal impairement has been found in other forms of chronic renal disease (86,87). Other studies, however, have found that deficient production of renal prostacyclin may be superior to increased urinary excretion of PGE2 as a marker to identify patients at risk for the toxic effects of NSAIDs (88). Deficient production of PGI2 as might occur in the setting of chronic glomerular disease or atherosclerotic cardiovascular disease may render the kidney more susceptible to NSAID-induced toxicity despite normal levels of constrictor hormones (89). In this regard, studies by Petrano and Ciabattoni et al., found that urinary excretion of PGE2 was elevated in patients with lupus but was no different from control values obtained in patients with other forms of chronic glomerular disease (88,90). By contrast,

all patients were found to have a significant reduction in the baseline urinary excretion of 6-keto-prostaglandin F1-alpha, the hydrolysis product of prostacylcin. After the administratin of ibuprofen, there was a significant inverse relationship between the observed reduction in renal blood flow and creatinine clearance and the basal values for urinary excretion of the prostacyclin metabolite (88,90). No such relationship was found between changes in renal function and urinary concentrations of PGE2. More recently, urinary PGE2 and 6-keto-PGF2 alpha were measured in 45 elderly patients with mild to moderate chronic renal failure (91). In this study, administration of naproxen was associated with a fall in urinary PGE2 but urinary excretion of 6-keto-PGF2 alpha remained unchanged. When renal function was examined, there was no change in the serum creatinine or creatinine clearance over the two weeks of the study. Other studies have confirmed this relationship in which preservation of prostacyclin metabolism in the face of NSAID administration is associated with stability of renal function (92,93). Only in patients who exhibit a decline in urinary 6-keto-PGF2 alpha levels does clinically evident renal failure develop. Since the urinary excretion of 6-keto-PGF1 alpha is reflective of PGI2 synthesis, the lack of decline in this urinary metabolite would suggest that the cortical synthesis of PGI2 is intact. The superiority of this marker as an indicator of renal tolerance to NSAIDs is most likely refective of the central role that PGI2 plays in preserving glomerular hemodynamics.

Another group that may be more vunerable to the toxic effects of NSAIDs is the elderly (94-97). This susceptability, in part, may be related to changes in renal function that normally accompany the aging process (98) (Table 6). Aging is associated with a progressive decline in the GFR and total renal blood flow. In addition, there is an increase in renal vascular resistance. Importantly, the renal vasculature becomes less responsive to vasodilators while the response to vasocontrictors remains intact. In an analysis of 1908 patients treated with ibuprofen, renal impairment was found to occur in 343 (18%) patients (95). The two most important risk factors identified for the develpment of toxicity was an age greater than 65 years and pre-existing renal insufficiency. In a prospective study of 114 elderly patients (mean age of 87 years) started on NSAID therapy,

Table 6. Predisposing factors for NSAID-induced nephrotoxicity in the elderly.

- Age-related changes in renal function
  - ↓ in GFR
  - ↓ in renal blood flow
  - ↑ in vascular resistance
- Age-related changes in pharmakokinetics
  - ↑ free drug concentration
    - -hypoalbuminemia
    - -retained metabolites
  - ↓ total body water
  - ↓ hepatic metabolism with longer drug 1/2 life

a greater than 50% increase in the serum urea nitrogen concentration was found in 15 (13%) patients (96). In this study, concurrent use of a loop diuretic and large doses of NSAIDs were found to be predictive of those who developed significant azotemia.

In additon to age related changes in renal function, age related changes in the pharmakokinetics of NSAIDs may also make this population more susceptible to renal toxicity (99,100). Elderly patients and in particular those with chronic illness often have lower albumin levels which reduce protein binding of the drugs and results in higher free drug concentrations. This binding of the parent compound to circulating albumin is further impaired by retained metabolites which accumulate as a result of the normal age related impairement in renal function. Increased drug levels also occur as a result of the age related decrease in total body water. Finally, decreased hepatic metaboism which is often present in the elderly contributes to a longer half life of the parent compound and can result in unexpectantly high drug levels.

Other conditions in which effective circulatory volume is normal or increased and yet renal function is critically dependent upon increased synthesis of prostaglandins include urinary obstruction (101), radiocontrast-induced injury (102), and administration of cyclosporine A (103). In each of these conditions the effects of vasoconstrictors synthesized intrarenally are counterbalanced by local production of vasodilatory prostaglandins. Administration of NSAIDs in each of these settings can be expected to result in an exagerated fall in renal function.

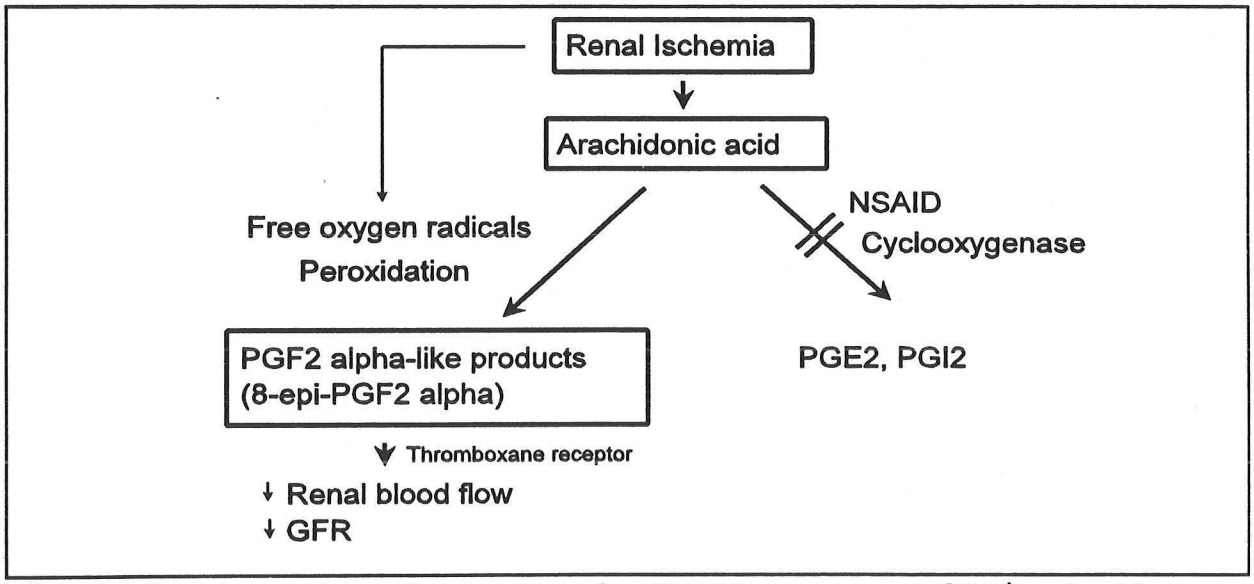


Figure 7. A novel pathway whereby NSAIDs may result in further vasoconstriction particularly in the setting of ischemia or inflammation.

An additional mechanism whereby NSAIDs may facilitate vasoconstriction and propogate ischemic renal injury has recently been proposed (99) (Figure 7). According to this proposal, inhibition of cyclooxygenase would allow a greater amount of arachidonic acid to be metabolized along a novel cyclooxygenase-independent pathway forming a series of potent vasoconstrictors. This pathway leads to the formation of a series of prostaglandin F2-like compounds by a mechanism involving the free radical-catalyzed peroxidation of arachidonic acid (104). One of these compounds, 8-epi-PGF2 alpha, has been found to be biologically active. In micropunture studies, infusions of this compound have been shown to result in a dose-dependent reduction in renal plasma flow and glomerular filtration rate (105). These changes were reversed in the setting of a thromboxane A2 receptor antagonist suggesting that the prostanoid acted principally through this receptor. According to this formulation, patients with ischemic or inflamatory renal injury would be particularly susceptible to the effects of NSAIDs not simply due to the lack of vasodilatory prostaglndins but also from the enhanced nonenzymatic formation of vasoconstrictor metabolites of arachidonic acid (99).

Are Certain NSAIDs Renal Sparing ?

A NSAID with effective anti-inflammatory properties but associted with less nephrotoxicity would be highly desirable since there is a sizable population at risk for renal toxicity. Salsalate is a nonacetylated salicylate which is commonly thought to be associated with less nephrotoxicity (106). This property, however, may simply be due to the fact that the drug is a weak inhibitor of prostaglandin synthesis as compared to other NSAIDs. In fact, at high doses of salsalate a dose dependent fall in the GFR and urinary excretion of PGI2 has been described (107).

Of much greater interest is the potential renal sparing properties of sulindac. This agent has been reported to be well tolerated in patients who had previously developed renal failure following the administration of naproxen or ibuprofen (108). In addition, sulindac, as compared to other NSAIDs, has been shown to neither reduce the urinary excretion of prostaglandins nor impair renal function in the setting of chronic glomerulonephritis (88), mild

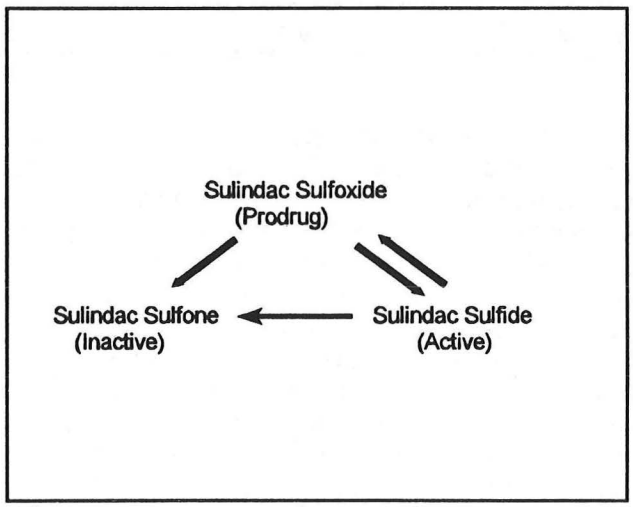


Figure 8. The kidney is capable of metabolizing sulindac sulfide into inactive metabolites.

to moderate chronic renal failure (109,110), congestive heart failure (111), and cirrhosis with ascites (112). It has been postulated that the renal sparing properties of sulindac are related to its unique metabolism. Sulindac is administered as a prodrug (sulindac sulfoxide) which must be first converted to sulindac sulfide in order to exert cyclooxygenase inhibitory effects. The sulfide metabolite can be converted back to the parent sulfoxide compound or be metabolized to an inactive sulfone metabolite (113) (Figure 8). The liver and kidney are thought to be the major sites at which each of these biotransformations take place. Based on the ability of the kidney to inactivate sulindac sulfide, renal prostaglandin sythesis should remain relatively intact (114). In fact, unlike other NSAIDs, the active metabolite of sulindac does not appear in the urine after oral administration of sulindac sulfoxide, but rather, is excreted as the parent compound or as the sulfone metabolite (108) (Table 7).

Table 7. Renal excretion of NSAIDs and active metabolites.

Drug	Renal excretion,%	Renal excretion products that are active,%	% original dose appearing as active drug in urine
Sulindac	44	0	0
Fenoprofen	94	4	3.8
Ibuprofen	66	8	5.3
Salicylates	80	10	8
Naproxen	95	10	9.5
Indomethacin	59	16	9.7
Tolmetin	99	10	9.9

Other studies, however, have tempered the initial enthsusiasm that sulindac is a renal sparing NSAID (115-123). The discreptantcy between these studies and those which reported no adverse renal affects may in part be explained by changes in the pharmakokinetics of sulindac which occur as a fucntion of duration of therapy and severity of underlying disease. Sulindac has a long half life (16-18 hours), which is prolonged in the setting of renal or liver disease. In either circumstance, the active compound, sulindac sulfide, can progressively accumulate in the plasma over several days to weeks. In the setting of chronic renal failure, steady state concentrations of ibuprofen are achieved within 24-48 hours whereas concentrations of sulindac sulfide may not achieve a steady state even after 11 days of therapy (116,117) (Figure 9). With regards to patients with baseline renal insufficiency, an adverse effect of sulindac on renal function has mostly been

reported in studies of longer duration which included patients with more advanced degrees of renal insuffiency (116,117). In this setting, levels of sulindac sulfide up to ten times normal have been reported (116). At these levels, it is possible that any potential renal sparing effect of sulindac is lost. Interestingly, in the isolated perfused kidney, urine prostaglandin excretion is not significantly affected when the perfusate sulindac sulfide concentration is close to therapeutic levels. By contrast, increasing the perfusate concentration to levels similar to that found in patients with advanced renal insufficiency will result in significant declines in urinary prostaglandin exctretion (113).

A similar pharmakokinetic mechanism may account for conflicting observations noted in patients with cirrhosis with ascites (112,118). In five patients who developed significant declines in both urinary prostaglandin excretion and glomerular filtration rate after the administration of sulindac, sulindac sulfide levels were found to be four times the level measured in six healthy controls (118). By contrast, a study which concluded that sulindac was renal sparing reported sulindac sulfide levels only 2.5 times those seen in healthy controls (112).

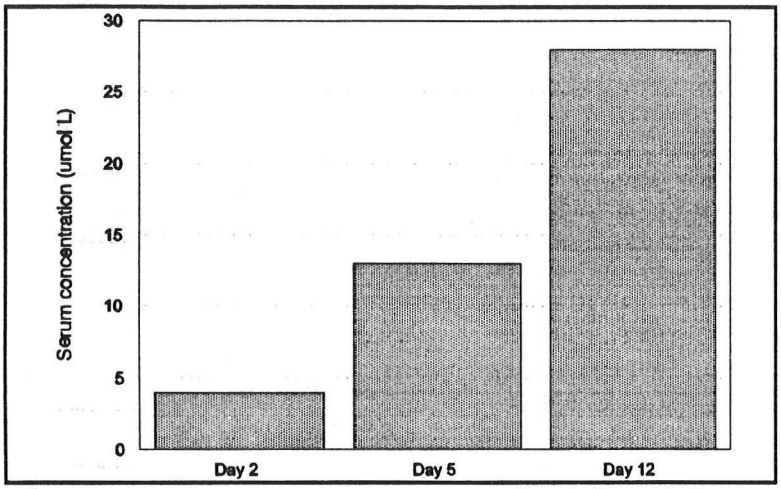


Figure 9 Mean serum concentration of sulindac sulfide in patients with CRF. Notice that a steady state level is not achieved after 12 days of 200 mg PO BID.

Thus, while there appears to be some reduced risk for vasoconstriction induced renal insufficiency in patients who take sulindac versus other NSAIDs, this agent still needs to be given with caution. It is likely that the renal sparing effect of sulindac may simply reflect that common clinical doses are at the low end of the dose response curve in terms of inhibiting renal prostaglndins. By contrast, similar doses administered to high risk patients, particularly those with renal insufficency or liver disease, may result in much higher sulindac sulfide levels which may be capable of inhibiting renal prostaglandin synthesis. In addition to disease-induced changes in the pharmakokinetics of sulindac, there may be individulal variability determined by genetic and/or environmental factors in the capacity of the kidney to convert sulindac sulfide to inactive metabolites (124). In this regard, a recent report found that 25 of 70 patients who were

chronically ingesting sulindac for treatment of arthritis had detectable sulindac sulfide levels in the urine. It is interesting to speculate that this subgroup may be the ones who are at risk for renal toxicity in the appropriate setting.

Another strategy which has been employed to decrease NSAID-induced renal insufficiency is to coadminister a prostaglandin analog such as misoprostol (125). In a double blind crossover study involving 10 patients with cirrhosis and ascites, administration of misoprostol tended to minimize the nephrotoxic effects of indomethacin but the results did not reach statistical significance. Whether such effects are sustained or observed in other clinical conditions dependent upon renal prostaglandin synthesis is unknown.

NSAID-Induced Chronic Renal Failure

The most common form of drug induced chronic renal failure is analgesic nephropathy. This lesion has most commonly been linked to the chronic ingestion of compound analgesics containing aspirn, phenacetin, and caffeine (126). Analgesic nephropathy occurs predominately in middle-aged women who tend to exhibit a characteristic psychological profile (127). A still unresolved question is whether long term use of NSAIDs can similarly result in a progressive and irreversible form of chronic renal failure.

In this regard, several NSAIDs have been associated with the development of papillary necrosis either when administerd alone or in combination with aspirn (128-135). In additon to inhibiting prostaglandin synthesis, the ability of these agents to redistribute blood flow to the cortex rendering the renal medulla ischemic may underlie this association (136,137). While the reports linking papillary necrosis and NSAIDs are predominately anectodal in nature, more recent observations would suggest that chronic renal failure resulting from long term use of NSAIDs may be more prevalent than once thought (138,139). In a multicenter case-control study Sandler et al., found a two fold increase in the risk for chronic renal failure associted with the previous daily use of NSAIDs (138). Chronic renal failure was newly diagnosed and was defined as a serum ceatinine concentration of 1.5 mg% or greater. This increased risk was primarily limited to older men. An additional report linking chronic use of NSAIDs with development of chronic renal failure described 56 patients from Australia (140). These patients had taken only NSAIDs over a period of 10 to 20 years for treatment of varying rheumatic diseases. In 19 patients (34%) radiographic evidence of papillary necrosis was found. In 37 patients renal biopsy material was available which disclosed evidence of chronic interstitial nephritis. The clinical characteristics of these patients was quite different from those with analgesic nephropathy caused by compound analgesics (Table 8).

Further evidence of chronic toxicity has been reported in a

preliminary communication in which patients treated with NSAIDs for rheumatoid arthritis and osteroarthritis were compared to a matched control arthritis population (141). In this study the NSAID-treated patients had a rise in the serum creatinine concentration from 1.28 mg/% to 2.58 mg/% over a mean period of 47.5 months. The control group not taking NSAIDs had stable renal function. Finally, Segasothy et al., reported on the risk of chronic renal disease in a prospective study of 259 heavy analgesic abusers (139). In this study, 69 patients developed radiographic evidence of papillary necrosis. Of these, 29 used NSAIDs either singularly (17 patients) or in combination with another NSAID (12 patients). Another 9 patients used NSAIDs in combination with paracetamol, aspirn, caffeine, or a traditional herbal medicine. Renal insuffiency (serum creatinine concentration 126-778 umol/L) was noted in 26 of the 38 patients who had used a NSAID chronically. Similar to the patients from Australia (140), this disorder was more common in males (1.9:1) distinguishing this disorder from classic analgesic nephropathy which typicaly occurs in females. Similarly, these patients did not exhibit the usual psychological profile associated with analgesic abuse.

Table 8. Differences in analgesic nephropathy before and after legislation(1979) and NSAID-induced CRF in Australia.

Characteristic	Analgesic neph 1972-74	Analgesic neph 1984-87	NSAID-induced CRF
#	100	100	56
Age (y)	49	62	69
Female:male	6.1:1	5.8:1	0.9:1
Typical psych. profile	Yes	Yes	No
Papillary necrosis (%)	92	90	34
CrCl <20ml/min (%)	40	20	5
UTI	34	22	2
Pelvic CA	0	6	0
Anemia (%)	40	13	6
Ischemic heart disease (%)	31	18	10

Thus, while further studies are needed to definitely assess the question of cumulative toxicity, it appears that some chronically treated patients may develop a change in renal function over a long

term. Given the abuse potential of powerful NSAIDs and the fact that ibuprofen and naprosyn are now available on an over-the-counter basis, it is possible that chronic NSAID abuse may become a more common cause of chronic renal failure in the future.

NSAID-Induced Glomerular and Interstitial Disease

The use of NSAIDs can be associated with the development of a distinct syndrome characterized by the development of interstitial nephritis and nephrotic range proteinuria. The incidence of this lesion is unknown but is thought to be rare. One estimate for fenoprofen induced interstitial nephritis was 1 case per 5300 patient-years of treatment (142). While virtually all NSAIDs have been reported to cause this syndrome, the vast majority of cases have been reported in association with use of the propionic acid derivatives (fenoprofen, ibuprofen, and naproxen) (142-151). Of these, fenoprofen has been implicated in greater than 60% of cases (152).

Unlike hemodynamically mediated acute renal failure, there are no clear cut risk factors which serve to identify those at risk for development of this syndrome. The mean age of patients is 65 years (152). The presence of an underlying renal disease prior to exposure of the NSAID has been notably absent.

This syndrome has generally been referred to as an example of acute interstitial nephritis. There are, however, a number of features which distinguish this form of interstitial renal disease from that which is observed with other pharmacologic agents (152,153) (Table 9). First, the average duration of exposure prior to the onset of disease is typically measured in months and can be as long as a year. By contrast, allergic interstitial nephritis due to other drugs usually presents within several days to weeks after exposure to the drug. Secondly, nephrotic range proteinuria is found in greater than 80% of cases of NSAID-induced interstitial disease, a degree of proteinuria which is distincly uncommon in acute allergic interstitial nephritis due to other drugs. Third, symptoms of hypersensitivity which are commonly seen in acute allergic interstitial nephritis such as rash, fever, arthralgias, or peripheral eosinophilia are uncommon in NSAID associated disease. Fourth, the vast majority of cases associtaed with NSAIDs have been reported in older patients. On the other hand, allergic interstitial nephritis is seen in all age groups.

Renal biopsy findings typically show a diffuse or focal lymphocytic infiltrate. The number of eosinophils in the infiltrate is variable but generally is not marked. In general, the glomeruli are normal by light microscopy. In some cases there is evidence of glomerulosclerosis. Since most patients who develop this syndrome are older, this finding may simply represent the normal age related increase in glomerulosclerosis. Immunofluorescent studies are typically nonspecific.

Table 9. Clinical characteristics of NSAID-induced tubulointerstitial nephritis (TIN) vs typical drug-induced TIN.

Characteristic	NSAID-induced TIN	Tyical drug-induced TIN
Duration of exposure	5d->1yr	5-26d
Hypersensitivity symptoms (%)	7-8	80
Eosinophilia (%)	17-18	75-80
Proteinuria >3.5gms/24h (%)	100	<10
Eosinophiluria (%)	0-5	80-85
Peak serum creatinine	1.5->10	3.7->10

There has been an occasional report of weak and variable staining for IgG, and C3 along the tubular basement membrane. Electron microscopy typically shows diffuse fusion of the podocytes in cases with heavy proteinuria. Mesangial electron dense deposits have only been observed in three patients suggesting that this is not an immune-mediated disease (154-156).

While the combination of interstitial nephritis and nephrotic syndrome is the most common clinical manifestation, a second presentation is the development of nephrotic syndrome without evidence of interstitial renal disease (153,157-159). Once again, the glomerular histology is typical of minimal change disease although two patients have been described with glomerular changes typical of membranous glomerulopathy (153). Interestingly, even in these two cases, the proteinuria resolved upon discontinuation of the drug. Six other cases of a membranous lesion have recently been reported in which withdrawl of the NSAID also resulted in resolution of the nephrotic syndrome (160). It is likely that the pathophysiologic mechanism which underlies the development glomerular disease in the absence of interstitial disease is similar, if not identical, to the more common finding of combined nephrotic proteinuria and interstitial nephritis.

A third presentation which has uncommonly been reported is the development of interstitial nephritis without nephrotic proteinuria (153,161-163). The onset of disease following the initiation of drug therapy tends to be much shorter and in this respect resembles the more common form of drug induced allergic interstitial nephritis. In addition, these patients commonly exhibit a systemic hypersensitivity reaction. Given the closer temporal relationship between the administration of the offending NSAID and the

development of renal insufficiency, one may confuse this syndrome with that of NSAID-induced vasomotor acute renal failure. Symptoms of hypersensitivity as well as histopathologic changes typical of interstitial renal disease should allow one to distinguish this lesion from hemodynamically mediated acute renal failure (Table 10).

Table 10. Characteristics of NSAID-induced vasomotor renal failure vs NSAID-induced interstitial nephritis.

Characteristic	Vasomotor ARF	Interstitial nephritis
Severity	Mild to moderate	Severe
Underlying renal disease	Yes	No
Time course to onset	Days	Wks to months
NSAID involved	All	Proprionic acid derivatives 75% (fenoprofen 61%)
Patients in hospital	Often	Outpatients
Proteinuria	Trivial	Nephrotic
Time to recovery	Prompt, No role for steroids	Wks to months, Steroids may help
Frequency	Common	Unusual
Urinary sodium	Low initially	High

Finally, NSAID toxicity may present as an exacerbation of an underly disease. In a case report of a patient with systemic lupus erythematosis, the development of interstitial nephritis and nephrotic syndrome after administration of naproxen clinically appeared as a rapidly progressive lupus glomerulonephritis (164).

The clinical course of patients who present in any one of these manners is to develop a spontaneous remission after removal of the offending NSAID. The time till resolution is variable but can range from a few days to several weeks. In some patients the degree of renal insufficiency can be severe enough that dialytic support is required. Steroid therapy has been used in many of the reported cases, however, the efficacy and necessity of this therapy is unknown. A reasonable approach is to reserve steroid therapy for those patients in which there has been no improvement in renal function after a period of 2-3 weeks of supportive care. It should be noted that relapses have been reported after inadvertent exposure to the same NSAID or after exposure to a different NSAID

(165-167).

The pathogensis of this disorder is unknown. A delayed hypersensitivity response to the NSAID has been suggested but the development of glomerular proteinuria remains difficult to explain. Another intriguing possibility involves the shunting of arachidonic acid metabolites to the lipoxygenase pathway resulting in production of leukotrienes under conditions of cyclooxygenase inhibition (168). Normally, however, there is negligible amounts of 5-lipoxygenase in renal tissue. If, however, NSAIDs lead to the development of a local immune response, influx of inflammatory cells would provide ample amounts of this enzyme for subsequent production of leukotrienes. These compounds are known to be capable of increasing vascular permeability and may therefore contribute to the leakage of protein across the glomerular cappilary wall (168).

NSAIDs and Sodium Balance

Sodium retention is a characteristic feature of virtually all NSAIDs, occuring in as many as 25% of patients who use them. The physiologic basis of this effect is directly related to the natriuretic properties of prostaglandins. When these compounds are administerd systemically or directly into the renal artery there is a marked increase in urinary sodium excretion (169,170). Evidence that endogenously synthesized prostaglandins are natriuretic comes from studies demonstrating that intrarenal infusion of arachidonic acid results in a similar increase in urinary sodium excretion, an effect which is abolished after administration of an inhibitor of prostaglandin synthesis (171,172).

Prostaglandins increase urinary sodium excretion by both indirect and direct mechanisms (Figure 10). Through their activity as renal vasodilators, prostaglandins may cause an increase in the filtered load of sodium. In addition, these compounds preferentially shunt blood flow to the inner cortical and medullary regions of the kidney (136,137). As a result of increase medullary blood flow, there is a fall in the medullary interstitial solute concentration. Processes that reduce the degree of medullary hypertonicity lead to a concommitant reduction in the osmotic withdrawal of water from the normally sodium impermeable thin descending limb of Henle. This, in turn, decreases the sodium concentration of fluid at the hairpin turn. The net effect is less passive reabsorption of sodium across the normally water impermeable thin ascending limb of Henle. Consistant with this mechanism, infusion of PGE1 lowers, and prostaglandin synthesis inhibition raises sodium chloride and total solute concentration in the medulla (173,174). Finally, prostaglandins can effect sodium reabsorption in the proximal tubule by virtue of their ability to influence the tone of the efferent arteriole. Changes in the tone of this vessel play a central role in determining the Starling forces that govern fluid reabsorption in this nephron segment

(175). Increased resistance of this vessel as which occurs in the setting of high concentrations of angiotensin II leads to a

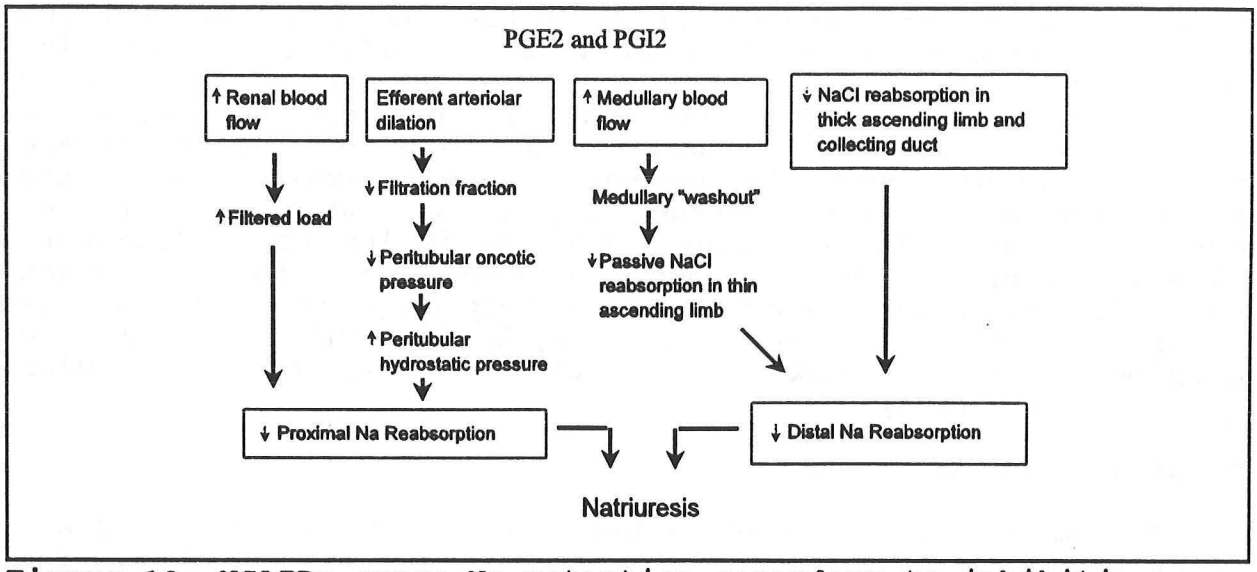


Figure 10. NSAIDs cause Na retention secondary to inhibiting these natriuretic properties of renal prostaglandins.

decrease in the downstream peritubular hydrostatic pressure. In additon, efferent constriction increases the filtration fraction by reducing glomerular plasma flow and increasing the upstream glomerular pressure. The increased filtration fraction leads to an increase in the peritubular oncotic pressure. A decrease in hydrostatic pressure and increase in oncotic pressure in the peritubular vessel favor fluid reabsorption in the proximal tubule. By modulating the degree to which the efferent arteriole is constricted and thus altering peritubuar Starling forces acting upon the proximal tubule, prostaglandins can decrease proximal tubular sodium reabsorption. Predictably, in a model of high circulating levels of AII induced by suprarenal aortic constriction, inhibition of prostaglandin synthesis was found to increase efferent arteriole oncotic pressure and decrease peritubular hydrostatic pressure resulting in a significant increase in proximal fluid reabsorption (175).

In additon to these hemodynamically mediated changes in renal sodium handling, prostaglandins have direct effects on tubular sodium transport. In the isolated perfused tubule, PGE2 has been shown to inhibit sodium transport in the cortical and outer medullary collecting duct (176,177). Using the same technique, PGE2 has also been shown to decrease chloride transport in the thick ascending limb of Henle (178). In vivo studies also support a direct inhibitory effect of prostaglandins on sodium transport in the loop of Henle, distal nephron, and collecting duct (179,180). The mechanism of this direct inhibitory effect is unclear, but may involve decreased activity of the Na-K ATPase pump (181,182).

Prostaglandins have also been shown to mediate the natriuretic response to increased renal interstitial hydrostatic pressure which occurs during renal interstitial volume expansion (183,184). In additon, these compounds play a permissive role in the sodium excretion that follows volume expansion and an increase in renal perfusion pressure (185-186).

By virtue of their natriuretic properties, prostaglandins play a role in ensuring adequate delivery of filtrate to more distal nephron segments under conditions in which distal delivery is threatened (e.g. renal ischemia, hypovolemia). Under such conditions, diminished NaCl reabsorption in the thick ascending limb of Henle reduces the energy requirements of this segment. This reduction in thick limb workload in conjunction with a prostaglandin mediated reallocation in renal blood flow help to maintain an adequate oxygen tension in the medulla under conditions that would otherwise have resulted in substantial hypoxic injury (188,189).

NSAIDs are thought to cause salt retention primarily by inhibiting prostaglandin synthesis and therefore disrupting the foregoing mechanisms. In addition, these compounds may have a direct mineralocorticoid effect (190,191). The extent to which salt retention becomes clinically manifest depends on the degree of baseline prostaglandin production. In normal healthy humans, baseline prostaglandin production is minimal. As a result, NSAID-induced positive sodium balance is transient and usually of no clinical importance. A markedly different response can be expected in clinical conditions in which basal renal prostaglandin synthesis is increased. In the setting of congestive heart failure,

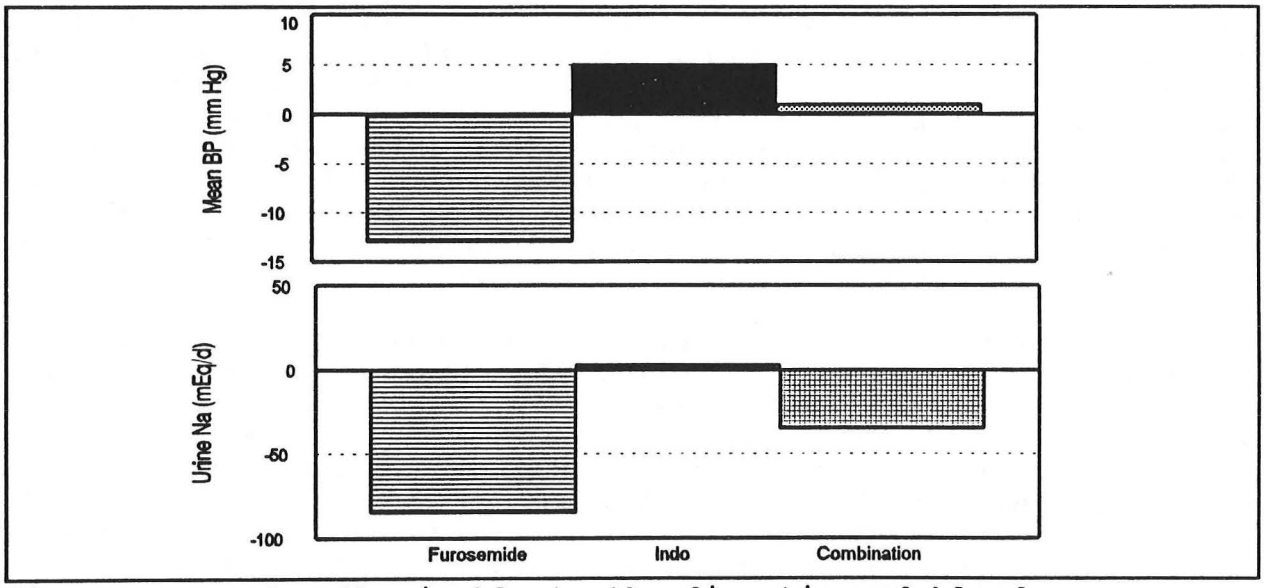


Figure 11. Indomethacin blunts the diuretic and blood pressure lowering effect of furosemide.

cirrhosis, or nephrosis the natriuretic properties of prostaglandins tend to moderate the avid salt retention that would otherwise occur in the setting of unopposed activation of the renin-angiotensin-aldosterone and adrenergic systems. The administration of NSAIDs in this setting can result in marked sodium retention and potentially adverse clinical consequences. A dramatic example of this effect is the report of a 70-year old man who gained 15 kg during a 17-day course of ibuprofen (192).

In additon to causing sodium retention, NSAIDs have been shown to attenuate the natriuretic effect of diuretics (193-196) (Figure 11). The mechanism of this resistance is multifactorial. The natriuretic effect of loop diuretics have, in part, been linked to the ability of these drugs to increase renal blood flow, an effect mediated by the stimulation of vasodilatory prostaglandins (197,198). By inhibiting prostaglandin synthesis, NSAIDs would limit sodium excretion by preventing the increase in renal blood flow normally seen after the administration of the diuretic. In dogs first rendered salt depleted, the natriuretic effect of furosemide is typically accompanied by renal vasodilation (197). If these salt depleted animals are pretreated with indomethacin, the vasodilatory response is blocked and the natriuretic effect is of smaller magnitude. On the other hand, there is no change in renal blood flow after the administration of furosemide in salt replete animals. Administration of indomethacin in this setting is without effect on the natriuretic response to furosemide. This finding is consistant with the clinical observation that diuretic resistance in association with NSAID use is most pronounced in salt retaining states (199-202). In this regard, the natriuretic effect of head out body water immersion following the administration of indomethacin is blunted in salt-depleted but not salt replete normal human subjects (203). In addition to this hemodynamic effect, micropuncture and microperfusion studies have shown that prostaglandin inhibition also blunts the effect of furosemide at the level of the thick ascending limb of Henle (204-206). This later effect may be related to inhibition of furosemide-induced stimulation of natriuretic prostaglandins which act within this tubular segemnt. Finally, NSAIDs may limit the diuretic reponse to loop diuretics by competing for tubular secretion thereby limiting the delivery of the drug to the luminal surface of the thick limb (207).

Indomethacin has also been shown to attenuate the diuretic response to hydrochlorothiazide (208). The mechanism of this interaction may result from enhanced salt absorption in the loop of Henle which would then limit the delivery of chloride to the thiazide's site of action in the distal nephron. A similar explanation by underlie the resistance which has been described with NSAIDs and spironolactone (209). It has also been suggested that NSAIDs may further interfere with spironolactone by competing for binding to the mineralocorticoid receptor (190,191).

In considering the natriuretic and vasodilatory properties of prostaglandins, it is not suprising that administration of NSAIDs have been shown to interfere with blood pressure control (Table 11). In pooled studies, administration of NSAIDs have been associated with an average increase in blood pressure of between 5 and 10 mmHg (210,212). Of the various subgroups examined, this effect is most pronounced in patients who are already hypertensive and much less so in those who are normotensive. Of the hypertensive patients, those treated with beta-blockers seem to be the most vunerable to the hypertensive effect of NSAIDs (210,212). In this regard, it is particularly interesting to note that propanolol has been shown to increase prostacylin formation (213). There is less of an interaction with diuretics and angiotensin converting enzyme inhibitors while no effect is seen with calcium channel blockers (210). Further subgroup analysis show that patients with low renin hypertension (elderly and blacks) are also at higher risk for this hypertensive effect. Interestingly, elderly hypertensive patients have been shown to have reduced urinary PGE2 excretion when compared to hypertensives of younger age (214). The pathogenesis of NSAID-induced hypertension is not known with certainty. In a recent meta-analysis, NSAIDs were found not to significantly alter body weight or urinary sodium excretion implying that mechanisms other than salt retention were reponsible for the increased blood pressure (212). In this regard, elimination of the vasodilator prostacyclin from the resistance blood vessels is believed to play some role in the development of hypertension in individuals at risk (215-217).

Table 11. Interaction of NSAIDs on blood pressure

- Greater effect in hypertensive patients
- 5-10 mm/Hg rise in BP
- Patients on diuretics and/or beta blockers most vunerable
- Calcium blockers less affected
- Elderly and Blacks greatest risk
- Mechanism
  -renal Na retention
  -peripheral effect

Renin Release, Hyperkalemia, and NSAIDs

The use of NSAIDs has been associated with the development of hyperkalemia in the setting of chronic renal insufficiency as well as normal renal function (218-223). The physiologic basis for this effect is inhibition of prostaglandin mediated renin release with subsequent development of hypoaldosteronism. Both in vivo and in vitro studies have shown a direct stimulatory effect of prostaglandins (primarily PGI2 and PGE2) on renin release from the juxtaglomerular cells (224,225). At the cellular level, this stimulation is mediated by an increase in intracellular cAMP with a decrease in intracelluar calcium as the final event. In addition to direct effects, these compounds play an essential intermediary role in those pathways which are of primary importance in the

regulation of renin release. In particular, renin release stimulated by both decreased perfusion pressure and decreased delivery of filtrate to the macula densa is dependent upon an intact cylooxygenase system (226,227). By contrast, beta adrenergic stimulation of renin release can occur independently of prostaglandin synthesis (228,229).

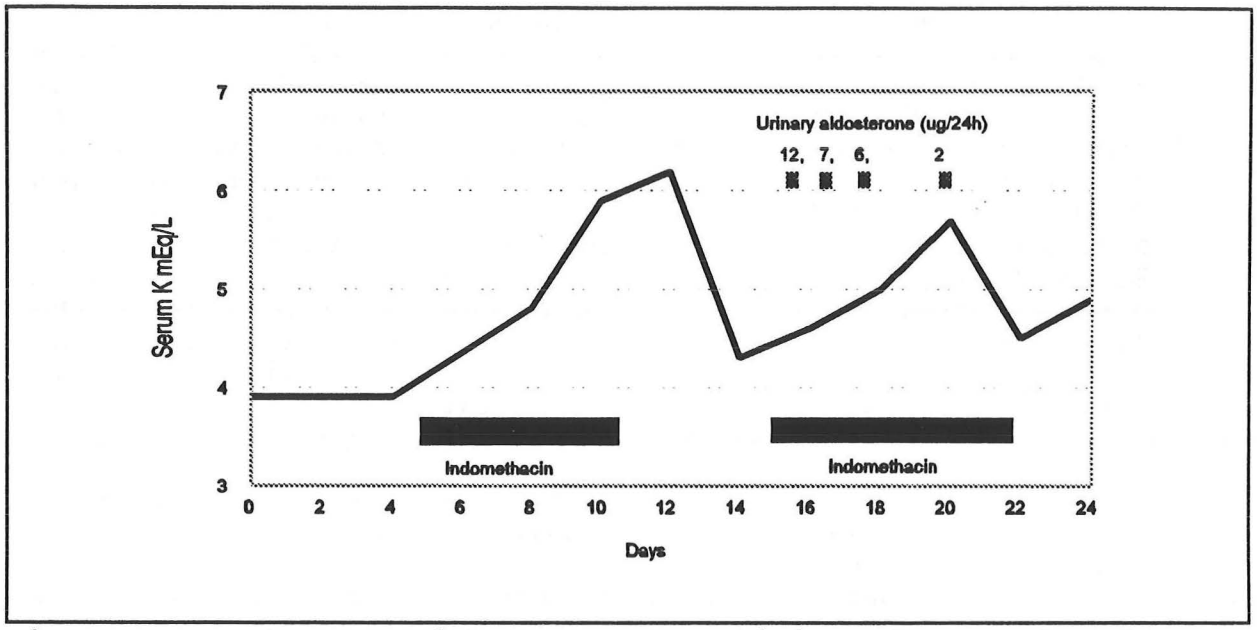


Figure 12. 37 yo man with a serum creatinine of 1.3 mg% and a CrCl of 112 ml/min. was treated with indomethacin for joint pain. He developed hyperkalemia with typical EKG changes. He was later rechallenged with indomethacin and urine aldosterone was measured before and during NSAID administration.

NSAID-induced suppresion of renin release with subsequent development of a hyporenin-hypoaldosterone state is thought to be the primary mechanism of hyperkalemia. Decreased renin release leads to decreasd circulating levels of angiotensin I which, in turn, results in low levels of AII. Since AII normally stimulates aldosterone release from the zona glomerulosa cells in the adrenal gland, serum aldosterone levels fall. In addition to low circulating levels, the effect of any given level of AII on aldosterone release is impaired since prostaglandins have been shown to play a intermediary role in the this stimulatory effect (230). Low circulating levels of AII further contribute to the development of hypoaldosteronism since adequate levels of AII are required for the stimulatory effect of hyperkalemia on aldosterone release (231). In addition to interfering with the renin-angiotensin-aldosterone cascade, NSAIDs favor positive potassium balance in other ways. As discussed earlier, inhibition of prostaglandin synthesis is associated with increased sodium reabsorption in the loop of Henle and thus decreased distal delivery. A reduction in sodium delivery to the aldosterone

sensitive cortical collecting tubule is a known factor impairing potassium excretion. In addition, tubular flow rates are an important determinant of potassium excretion. Since NSAIDs increase the hydroosmotic effect of AVP, flow rates can fall, further impairing potassium excretion. Finally, decreased synthesis of prostaglandins may have effects of decreasing potassium secretion at the level of the potssium channel (98,232).

The development of hyperkalemia in patients receiving a NSAID is most likely to occur in the setting of renal insufficiency or those with baseline abnormalities in the renin-angiotensin-aldosterone system (223). Diabetic patients are at risk due to the increased incidence of hyporeninemic hypoaldosteronism which occurs in this patient population (233,234). Similarly, the elderly are at higher risk by virtue of the normal age related decrease in ciculating renin and aldosterone levels (98,235). Particular caution should be used when NSAIDs are combined with other pharmacologic agents known to interfere with the renin-angiotensin-

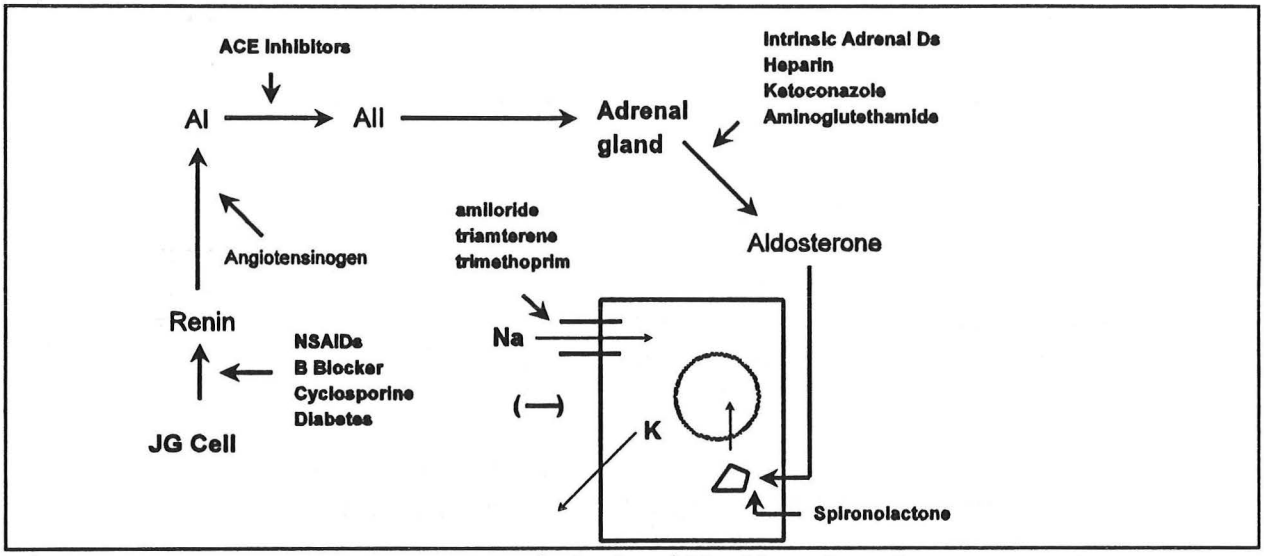


Figure 13. NSAIDs are associated with the development of hyporeninemic hypoaldosteronism and hyperkalemia.

aldosterone cascade (Figure 13). Examples would include beta blockers, angiotensin converting enzyme inhibitors, heparin, ketoconozole, high dose trimethoprim, and potassium sparing diuretics (236,237).

Water Metabolism and NSAIDs

Prostaglandins have important modulatory effects on renal water metabolism. Their primary effect is to impair the ability to maximally concentrate the urine. In doing so, two processes which are central in the elaboration of a concentrated urine are

interfered with, namely, the generation of a hypertonic interstitium and maximal collecting duct water permeability. The decrease in interstitial hypertonicity is due to a washout effect which results from the ability of prostaglandins to shunt blood flow to the inner cortical and medullary regions of the kidney (136,137). In addition, prostaglandins decrease sodium absorption in the thick ascending limb and decrease AVP-induced urea permeability in the medullary collecting duct. Decreased accumulation of sodium and urea in the interstitium further reduces the interstitial osmolality. The impairement in collecting duct water permeabiity is the result of prostaglandins opposing the hydroosmotic effect of AVP (238-240). Interestingly, AVP is known to stimulate PGE2 synthesis in collecting duct cells; by doing so, AVP induces its own antagonist. This interaction is another example in which prostaglandins exert a moderating effect on an effector mechanism which elicited their synthesis. In this case, prostaglandins play an important role in minimizing the water retention that would otherwise occur if the activity of AVP were unopposed (241). By opposing the vasocontrictive action of AVP, prostaglandins also contribute to the maintenance of glomerular perfusion and filtration (242).

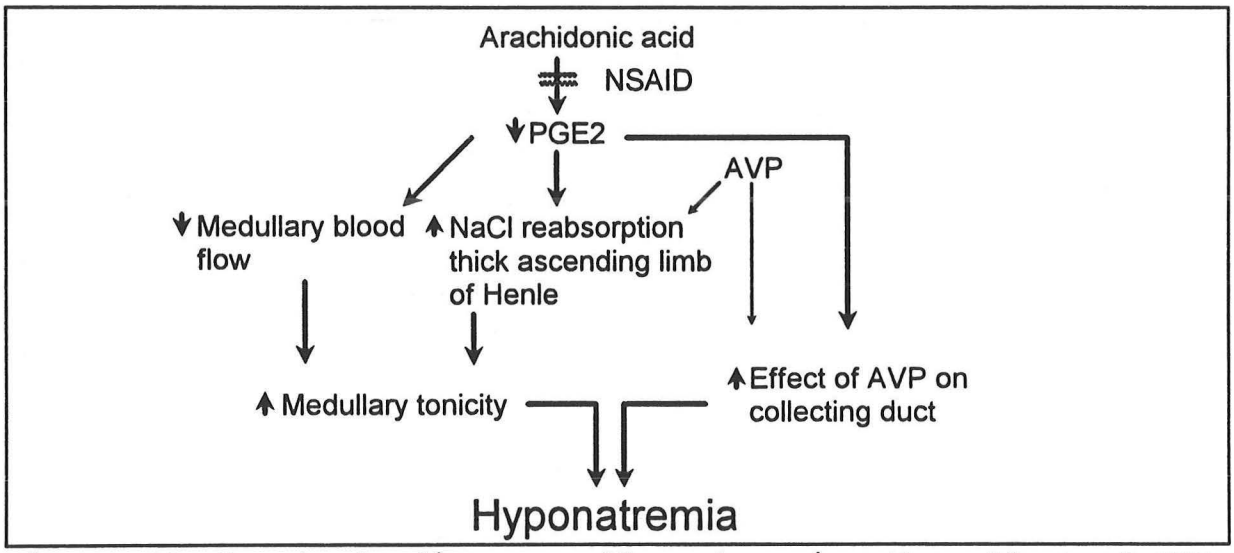
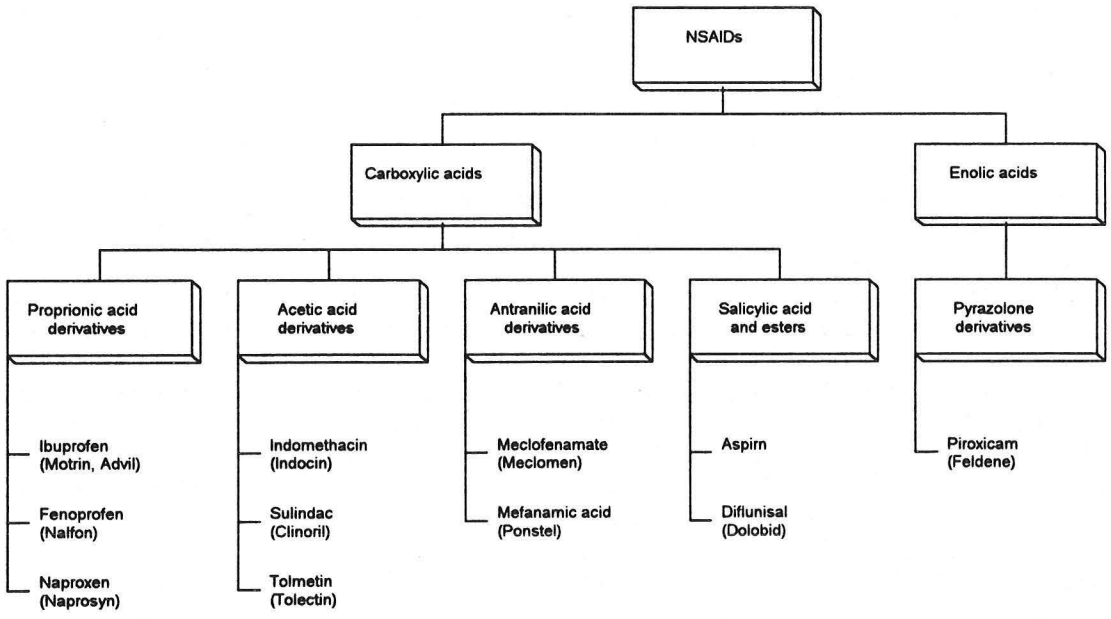


Figure 14. Prostaglandins normally antagonize the effect of AVP to increase NaCl reabsorption in the thick ascending limb of Henle and water absorption in the collecting duct.

Based on the foregoing discussion, administration of NSAIDs would predictably impair free water excretion by increasing the hydroosmotic effect of any given level of circulating AVP and increasing the degree of interstitial hypertonicity (Figure 14). In most circumstances, however, hyponatremia is not associated with the use of NSAIDs. Under normal conditions, any decrease in serum

osmolality would be sensed in the hypothalamus and result in inhibition of AVP release. As a consequence, exess free water would be promtly excreted restoring the serum osmolality back to normal. On the other hand, administration of NSAIDs in the setting of non-suppressable AVP release may result in dramatic falls in the serum sodium concentration. Patients at risk for this complication would include those with high circulating levels of AVP driven by a decreased effective circulatory volume such as congestive heart failure or cirrhosis (243). Patients with SIADH or those taking medications capable of stimulating AVP secretion or impairing urinary dilution by other mechanisms are also at risk for the development of hyponatremia (70,244).

Chemical Classification of NSAIDs



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