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RENAL TOXICITY OF THE NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) or the aspirin-like drugs may produce either acute, reversible, or permanent renal toxicity and a variety of effects on electrolyte and water homeostasis (1, 2; Table 1). Acute ischemic renal insufficiency occurs within hours of the initial doses of NSAIDs in susceptible persons and is readily reversible upon withdrawal of the offending NSAID. The mechanisms for the acute renal effects on the kidney are understood. In contrast, permanent damage to the kidney has occurred in persons who have abused analgesic mixtures for many years, particularly those containing phenacetin. The mechanism of this analgesic-associated nephropathy is poorly understood. Although several reports have appeared implicating the newer NSAIDs as a cause of analgesic-associated nephropathy, such reports are sparse. It is entirely possible that the acute, reversible effects of NSAIDs on the kidney and their chronic, irreversible renal effects share a common causal pathway, but evidence to support such a link has not been forthcoming (3). Independent of their ability to cause acute and chronic renal impairment, NSAIDs may affect sodium and potassium homeostasis and water metabolism. Finally, NSAIDs may interfere with antihypertensive medications and thus result in poorly controlled blood pressure. This review describes the renal toxicity of the NSAIDs, focusing on those causing a decreased glomerular filtration rate.

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Table 1 Renal effects of NSAIDs

Allergic-type interstitial nephritis
Secondary to inhibition of renal prostaglandins
• Sodium retention
• Water retention
• Hyporeninemic hypoaldosteronism
• Acute ischemic renal failure
Analgesic nephropathy
Urate nephropathy

From a public health perspective, the putative renal toxicity of the NSAIDs is consequential because of their widespread availability and use. In the United States, 18 nonsalicylate NSAIDs are now available to consumers who receive over 70 million NSAID prescriptions annually at a cost exceeding $1 billion (4). Although the use of older NSAIDs, particularly phenylbutazone and indomethacin, has decreased since 1973, the overall prevalence of nonsalicylate NSAID use more than doubled from about 30 million prescriptions in 1973 to over 60 million in 1981 (5). Since 1987, the use of prescription NSAIDs appears to have stabilized at about 70 million prescriptions per annum. In 1984, ibuprofen became the first nonsalicylate NSAID available OTC. Additionally, there are over 70 aspirin and salicylate products, many available over-the-counter (OTC). Presently, the pharmaceutical industry has great interest in expanding the OTC market to include prescription products with pending patent expirations (6). However, concern about the renal effects of potent NSAIDs available OTC has been raised by the Ad Hoc Committee for the National Kidney Foundation; the incorporation of specific warnings into package labeling has been suggested (7).

Of particular concern is that those with the greatest need for continuous NSAID therapy may also be at greatest risk, namely elderly persons (8). The highest prevalence of both arthritis and its associated disability (the major indication for chronic NSAID therapy) and renal impairment (a putative risk factor for NSAID-associated renal insufficiency) is among elderly persons (9, 10). Their use of NSAIDs is more than 3.5 times greater than their younger counterparts (4). Our own survey of elderly persons living in urban public housing complexes revealed that NSAIDs were the most frequently used OTC and prescription drugs (11). Worldwide statistics from 1987 regarding NSAID use and sales of NSAIDs (including the USA) revealed that three of the top 10 most-used drugs were NSAIDs and that their sales had increased 21% from 1986 to 1987 (12). Thus, the high prevalence of NSAID use and widespread availability heightens concerns about the renal safety of the NSAIDs.

RENAL PHARMACOLOGY OF NSAIDs

Despite the widespread use of NSAIDs and the length of time they have been available for clinical study, large gaps exist in our understanding of their pharmacokinetics and pharmacodynamics in humans (8). For example, early studies of NSAID disposition measured total drug concentration, whereas such results may be misleading in terms of the pharmacokinetics of the unbound, pharmacologically active drug. Similarly, it has recently become clear that with some NSAIDs, particularly the arylpropionic acid class, activity towards inhibition of prostaglandin synthesis resides in the (S)-enantiomer (14). For the most part, prior studies of disposition and response have not differentiated between active and inactive forms. Overall, these new considerations have compromised the usefulness of most information in the earlier literature (8).

Pharmacokinetics

Table 2 contains the chemical classification of the NSAIDs and their pharmacokinetic characteristics (for review see Refs. 15–17). These characteristics include: (*a*) small volume of distribution; (*b*) extensive protein binding, (*c*) variable intrinsic clearance; (*d*) low urinary excretion of parent drug; and (*e*) variable half-life. The drugs appear to be well absorbed though absolute bioavailability has been determined for only a few NSAIDs. Either the parent drug or the active metabolite is typically a weak acid that is avidly bound to plasma proteins, especially albumin. As a result, the NSAIDs have relatively small volumes of distribution, approximating plasma volume for most. Fenbufen, sulindac, and nabumetone are metabolized to active metabolites. The drug or active moiety is extensively metabolized primarily by hepatic oxidation or glucuronidation. Consequently, for most NSAIDs, little active compound is eliminated into the urine.

Two other dispositional aspects of the arylpropionic acids have recently become apparent; (*a*) formation of acyl-glucuronides, and (*b*) in vivo transformation of the inactive enantiomer into the eutomer. The arylpropionic acids are characterized by formation of acyl-glucuronide conjugates that are unstable and can be readily cleaved back to the parent drug (17). This phenomenon can result in a so-called "futile cycle" wherein a NSAID with negligible renal elimination accumulates in patients with renal insufficiency. Several NSAIDs, for example, ketoprofen and ketorolac, are excreted predominantly as acyl-glucuronides via the kidney. In patients with renal insufficiency, the glucuronide conjugate accumulates and they hydrolyze to reform the parent drug. The net effect of this process is accumulation of the parent drug (15, 18) in patients with renal insufficiency even though the parent drug itself is not eliminated by the kidney.

The importance of examining the disposition of the separate enantiomers

Table 2 Classification and pharmacokinetic characteristics of NSAIDs

Class and members	Volume of distribution (liter/kg)	Plasma protein binding (%)	Clearance (ml/min/kg)	Urinary Excretion (%)	Half-life (hours)[a]
Salicylic Acid Derivatives					
Aspirin[b]	0.15	85–90	9.3	<2	0.25 ± 0.03
Salicylate[c]	0.17	80–95[d]	0.14–0.86	2–30[e]	2–19[f]
Diflunisal	0.10	99.9	0.11	3–9	13 ± 2
Arylacetic Acids					
Alclofenac[g]	0.10	>99	1.5–2.5	10–50	1.5–2.5
Diclofenac	0.12	>99.5	3.7	<1	1.1 ± 0.2
Arylpropionic Acids					
Benoxaprofen		>98	0.03–0.14	<5	25–32
Carprofen		>99	0.29–0.57	3–5	9–16
Fenbufen	2–4	>98	2.1–3.6	<2	8–17
Active metabolites:					
γ-hydroxy-4-biphenyl butanoic acid				<3	7–17
Biphenyl-4-acetic acid				1–15	7–12
Fenoprofen	0.10	>99	0.6–1.3	30	2.5 ± 0.5
Flurbiprofen	0.10	>99	0.3	<1	3.8 ± 1.2
Ibuprofen	0.1–0.15	>99	0.6–1.4	<1	2.0 ± 0.5
Ketoprofen	0.11	>99	1.2	<1	1.8 ± 0.3
Naproxen	0.10–0.12	>99	0.07–0.14	<1	14 ± 2
Oxaprozin[g]	0.16	>99	0.04	1–4	58 ± 10
Pirprofen		>99		<5	7.1 ± 1.2
Suprofen	0.17	>99	1.4–1.8	<1	1–3
Tiaprofenic Acid	0.1–0.25	98	0.6–1.4	<5	3 ± 0.2
Heterocyclic Acetic Acids					
Etodolac	0.4	>99	0.68	<1	6.5 ± 0.3
Indomethacin[g]	0.3–1.6	>99	1–2	16	4.6 ± 0.7
Ketorolac[g]	0.1–0.25	>99	0.36–0.57	58	4–10
Sulindac		>99		7	8
Active Metabolite					
Sulindac sulfide	2	93.1	1.5	<1	15.8 ± 11.6
Tolmetin	0.04	>99	1.8	7	1.0 ± 0.3
Zomepirac	1.8	98.5	2.6	0–5	4–8
Pyrazolones					
Azapropazone[g]	0.14	>99		62	15 ± 4
Oxyphenbutazone	0.17	>98	0.02	<2	27–64
Phenylbutazone	0.17	>99		1–3	68 ± 25
Oxicams					
Isoxicam	0.17	96	0.001	1–2	29–34
Piroxicam	0.12–0.15	>99	0.04	4–10	57 ± 22
Tenoxicam	0.12–0.15	>98	0.0014	<1	60–75
Fenamic Acids					
Flufenamic acid		>90		<1	9

Table 2 (*continued*) Classification and pharmacokinetic characteristics of NSAIDs

Class and members	Volume of distribution (liter/kg)	Plasma protein binding (%)	Clearance (ml/min/kg)	Urinary Excretion (%)	Half-life (hours)[a]
Mefenamic acid	1.3	>99		<6	3–4
Meclofenamic acid		99	2.6–2.9	2–4	3
Nonacidic Drugs					
Nabumetone					
Active Metabolite:					
6-methoxy-2-naphyl-acetic acid	7.5	99		1	26 ± 5

[a] Mean ± S.D. or upper and lower bounds of the range. [b] Acetylated; hydrolyzes rapidly forming salicylate. [c] Includes: benorylate, salsalate, and the choline, magnesium, and sodium salts. [d] Decreases as plasma concentration increases. [e] Increases as urinary pH increases. [f] Increases as plasma concentration increases. [g] Drugs with clinically important renal elimination. (Compiled using references 15–17.)

of ibuprofen has only recently become apparent. Ibuprofen and other arylpropionic acids have an asymmetric carbon; each therefore exists as two distinct enantiomers (13). Interestingly, after an oral dose of racemic ibuprofen, stereoselective serum concentration measurements indicate greater amounts of circulating (S)-ibuprofen. Thus, by some mechanism, enrichment in the S-enantiomer occurs. Recent studies have shown that this is the result of a unique in vivo chiral inversion from the inactive (R)− to the active (S)+ enantiomer (13). Clearly, earlier data measuring only racemic ibuprofen would be misleading as to concentrations of active stereoisomers.

Pharmacodynamics

NSAIDs produce most of their therapeutic and adverse effects through inhibition of prostaglandin (PG) synthesis (Figure 1). Each of the three arms of the arachidonic acid cascade—the cyclooxygenase, cytochrome P-450 monooxygenase, and lipoxygenase pathways—affects some aspect of renal hemodynamics or tubular function. Supposedly, interruptions in one pathway could produce increased amounts of substrate available to other pathways. For example, blocking cyclooxygenase with NSAIDs could provide greater amounts of substrate to the P-450 pathway (increasing production of epoxides and omega oxidation products) or the lipoxygenase pathway (increasing production of leukotrienes) (19, 20). Shifts in the metabolic transformation of prostaglandins by differential inhibition of one pathway over another could result in a variety of renal effects, including toxicity. The functional significance of the metabolites of arachidonic acid and the impact of NSAIDs upon renal physiology are discussed further below.

The mechanism by which NSAIDs inhibit cyclooxygenase is stereo-selective. This is particularly important in considerating the renal pharmacodynam-

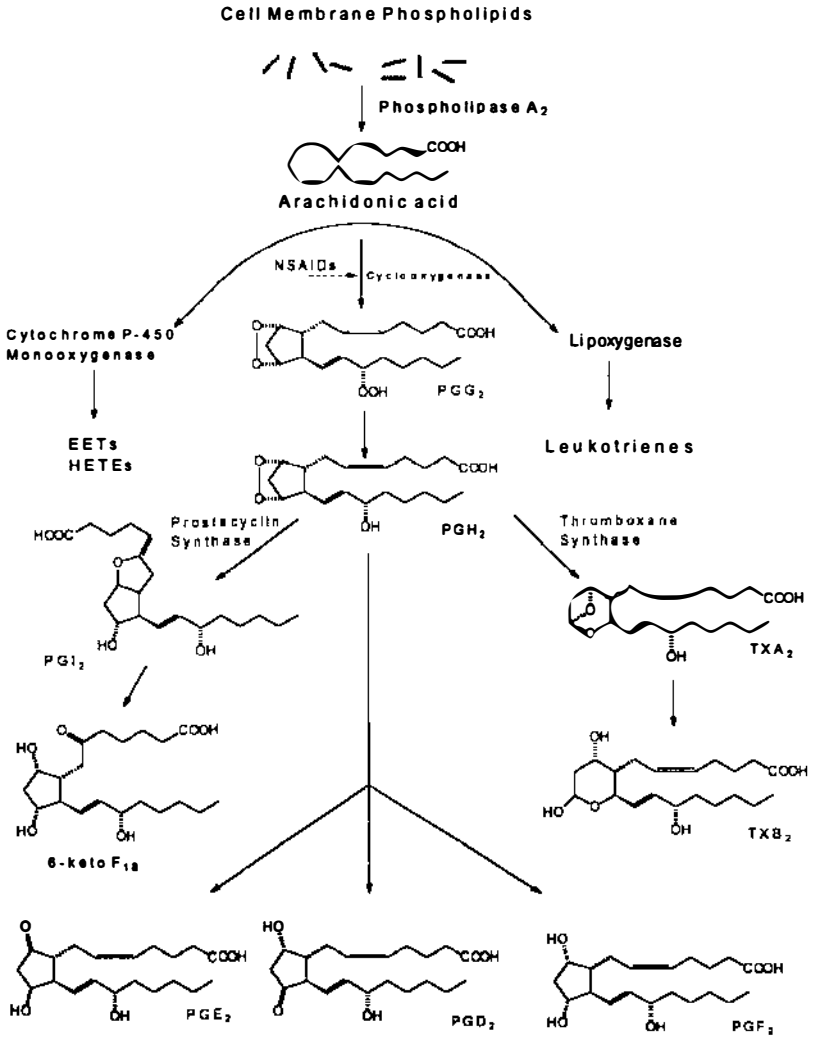

Figure 1 Metabolic pathways of the arachidonic acid cascade. NSAIDs: Non-steroidal anti-inflammatory drugs; EETs: epoxyeicosatrienoic acids; HETEs: hydroxyeicosatetraenoic acids; PG: prostaglandin; TX: thromboxane.

ics of the arylpropionic acid NSAIDs such as ibuprofen (Table 2). For these, the ability to inhibit cyclooxygenase resides almost entirely in the (S)+ enantiomer and data available on the disposition of this active form, particularly its unbound concentrations, are meager (8, 13). Although some work has been done using the isolated perfused kidney (21–23), we have little

insight into the integrative renal effects of the (S)+ enantiomer or its (R)− antipode in humans.

Finally, recent data suggest that unstable acyl-glucuronides migrate to form stable covalent bonds with plasma proteins such as albumin (24–26). Formation of the adduct for fenoprofen is a stereochemical process (24). Theoretically, these macromolecular complexes could then act as haptens that cause idiosyncratic renal toxicity; this phenomenon could account, at least in part, for the seemingly high prevalence of acute interstitial nephritis with fenoprofen.

NEPHRON STRUCTURE AND FUNCTIONAL SIGNIFICANCE FOR NSAID TOXICITY

The renal effects of the NSAIDs are best understood by examining the structure of the nephron, its capacity to produce a variety of autacoids, and the normal physiology of these autacoids throughout the nephron and interstitium.

Nephron Structure

Figure 2 shows the nephron and the compartmentalization of autacoid production (27, 28). Because renal impairment from NSAIDs occurs most frequently because of their renal hemodynamic effects, understanding the renal vasculature is important. Branching from the arcuate artery is the afferent arteriole, the vessel that enters the glomerulus. The afferent arteriole is surrounded by juxtaglomerular cells and lies adjacent to the macula densa contained within the distal convoluted tubule. Together this arrangement is referred to as the juxtaglomerular apparatus (JGA). JGA sensors within the distal tubules control glomerular hemodynamics through glomerulotubular feedback and also control potassium homeostasis through renin release, which is, in part, governed by prostacylin or PGI_2 (28, 29). Upon entering the glomerulus, the afferent arteriole divides into four to six capillary tufts that are supported by a network of mesangium and associated mesangial matrix (30, 31). The mesangium has multiple functions besides providing support. The cells of the mesangium are similar to smooth muscle cells in that they can expand and contract in response to circulating autacoids or in response to activity at the polar cushion of the afferent arteriole. The mesangial matrix is exposed to many of the constituents found in blood and can absorb proteins and macromolecules (unlike the tubular system of the nephron) (31).

The glomerular shell, called Bowman's capsule, is an extension of the proximal tubule. The capsule contains the normally protein-free filtrate that ultimately forms the urine. Sieving properties and electronegativity of the glomerular endothelium determine the amounts of high-molecular weight

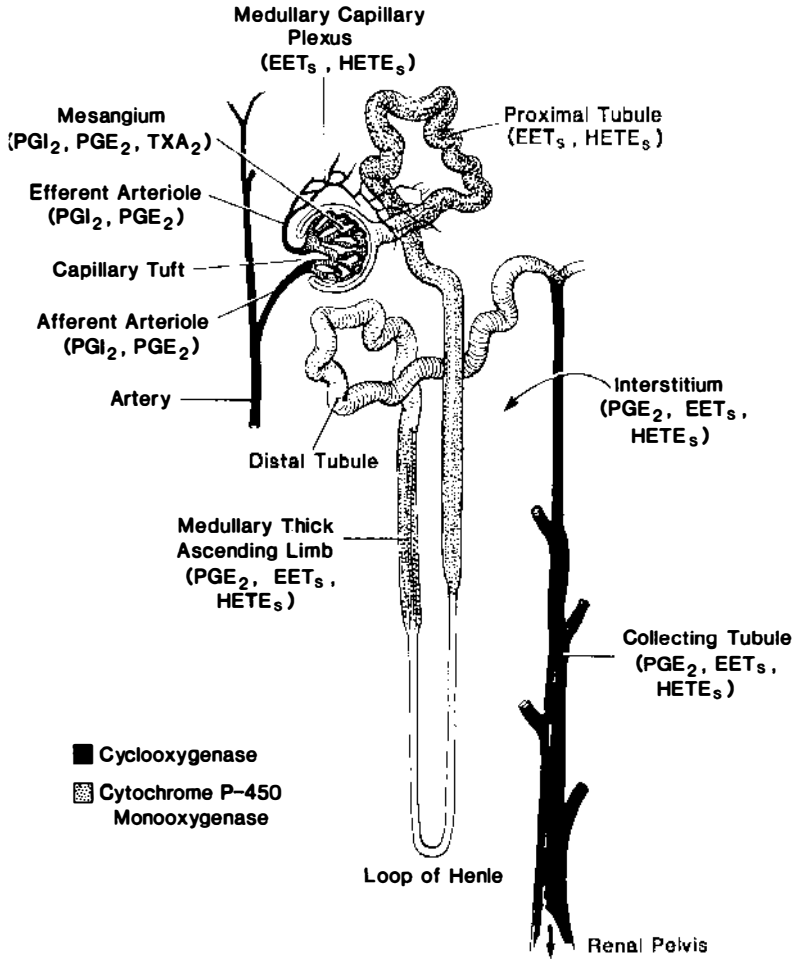

Figure 2 Distribution of renal autacoids within the nephron vasculature and tubular structures. Abbreviations are the same as for Figure 1.

substances such as proteins that appear in urine. The efferent arteriole, the vessel that leaves the glomerulus, contains the effluent. The efferent arteriole descends deep into the interstitium forming the medullary capillary plexus and vasa recta. These latter vessels exchange water and electrolytes and provide oxygen and nutrients to the medulla.

Staining techniques have revealed synthesis of prostaglandins, thromboxane, and arachidonic acid metabolites of cytochrome P-450 monooxygenase throughout the renal vasculature and tubules (Figure 2; 28, 32). As seen in

the figure, cyclooxygenase is present throughout the vasculature including the afferent and efferent arterioles, the glomerular capillary tuft, and also the collecting tubule. It has recently become apparent that cytochrome P-450 monooxygenase is present in the proximal tubule and the medullary thick ascending loop of Henle (19). Thus, products of cytochrome P-450 monooxygenase may be formed de novo or prostaglandins derived from the vasculature may become substrates at sites distal to the glomerulus, such as within the medullary tubules and interstitium. Metabolites of this P-450 system include epoxides of arachidonic acid such as epoxyeicosatrienoic acids (EETs), and hydroxyeicosatetraenoic acids (HETEs) and omega oxidation products (19).

Functional Significance of Renal Autacoids

Renal autacoids have a variety of physiologic effects within the kidney. Prostaglandins are crucial for the maintenance of renal perfusion in situations associated with reduced actual or effective circulating volume, and influence sodium and potassium homeostasis, and water metabolism (Table 3). The anatomic sites of production predict the inherent activity of prostaglandins and their metabolites (32, 33). For example, PGI_2 is predominately found in the glomerulus and is the primary prostaglandin affecting glomerular hemodynamics (34).

Although certain endothelial-derived autacoids such as nitric oxide (NO) and endothelin-1 (ET-1) balance renal hemodynamics in both sickness and in health, prostaglandins play only a minor role in renal hemodynamics in the healthy person (2, 35–37). However, when renal perfusion is rendered prostaglandin-dependent, administration of NSAIDs can cause immediate decrements in renal plasma flow and glomerular filtration that can result in an hypoxic insult to the kidney.

The net effect of prostaglandins on renal perfusion is the result of interactions among a variety of substances upon the renal vasculature. Angiotensin II (AII) has little effect at the afferent arteriole or within the capillaries of the glomerulus unless systemic concentrations are quite high (38). In contrast, the efferent arteriole is exquisitely sensitive to the effects of AII. This preferential vasoconstriction of the efferent arteriole provides hydraulic auto-regulation of glomerular filtration. The vasoconstrictive effects of AII are counterbalanced primarily by PGI_2, and to a lesser extent, PGE_2 (28, 33, 34). Other vasoconstrictive substances include platelet-derived thromboxane A_2 (TXA_2), vasopressin, ET-1, and catecholamines such as norepinephrine (36, 37). Our understanding of the direct and interacting effects of NO is evolving. It is clear, however, that this ubiquitous vasodilator also plays an important role in renal dynamics (35).

The mesangium is richly endowed with vasoactive substances such as PGI_2,

Table 3 Effects of renal autocoids in the kidney[a]

Location	Autacoid	Response
Glomerular Arterioles		
Afferent	PGI_2	Dilation
	PGE_2[b]	Dilation
	NO	Dilation
	ET-1	Constriction
	NE	Constriction
Efferent	PGI_2	Dilation
	NO	Dilation
	AII	Constriction
	ET-1	Constriction
	NE	Constriction
Capillary tuft[c]	PGI_2	Dilation
	NO	Dilation
	ET-1	Constriction
	NE	Constriction
Glomerular Mesangium[d]		
	PGI_2	Relaxation
	PGE_2	Relaxation
	NO	Relaxation
	ET-1	Contraction
	TXA_2	Contraction
	[Cytokines, PDGF, EGF, IL-1]	[Cell growth and histologic changes]
Proximal tubule (S_1 segment)		
	5,6-EET	Inhibition of Na^+-K^+-ATPase
	12(R)-HETE[e]	
	20-HETE	
Loop of Henle		
Thin segment	None	—
Thick ascending limb	5,6-EET	Inhibition of Na^+-K^+-ATPase
	12(R)-HETE[e]	
	20-HETE	
	PGE_2	
	PGG_2	
	PGH_2	
Distal tubule		
	None — low PGE_2	—
Juxtaglomerular Apparatus		
	12(R)-HETE[e]	Renin release
	PGI_2	
Collecting tubule, interstium, and Vasa Recta		
	PGE_2	Inhibition of ADH or AVP
	12-(R)HETE	Vasodilation
	PGE_2	

PGE_2, and intrinsic TXA_2 (30). The effects of these autacoids and a variety of macrophage and monocyte metabolites such as cytokines, interleukins, and cell-growth factors affect glomerular morphology and pathology. In summary, renal blood flow is controlled by the effects of a variety of autacoids upon the glomerular vasculature and mesangium. It should therefore be apparent that NSAIDs can affect renal function by interaction with the glomerular vasculature and that urinary excretion of active drug is not a requisite to elicit toxic effects.

Renin release is also partially controlled by PGI_2 (32, 33). Inhibition of prostaglandin synthesis with the administration of a NSAID can therefore affect the renin-angiotensin-aldosterone system. Reduced renin synthesis causes a reduction in aldosterone secretion resulting in type IV renal tubular acidosis (1, 2, 29). The most prominent clinical manifestation of this syndrome of hyporeninemic-hypoaldosteronism is hyperkalemia, especially in patients with pre-existing renal impairment.

PGE_2 is the predominant prostaglandin produced in the collecting tubule and within the interstitium and is the primary prostaglandin affecting medullary hemodynamics, and sodium and water metabolism (32, 33). Prostaglandins have natriuretic effects (39). Natriuresis is the result of two effects of prostaglandins: first, prostaglandins cause vasodilation, which increases renal blood flow and thereby reduces proximal reabsorption of sodium (39); second, prostaglandins directly inhibit sodium reabsorption at the thick ascending limb of the loop of Henle (40). Hence, administration of NSAIDs can cause both sodium retention and blunting of the response to diuretics (39–41). In most persons, the sodium-retentive effects of NSAIDs are not clinically discernable. However, in patients prone to sodium retention, such as those with chronic renal insufficiency or heart failure, sodium retention can result in weight gain, edema, and can interfere with the effects of antihypertensive drugs (see below).

Cytochrome P-450 metabolites of prostaglandins also produce natriuresis. HEETs are predominately found in the proximal tubule and the medullary thick ascending limb of the loop of Henle and their primary effect is inhibition of Na^+-K^+-ATPase at the S1 segment of the proximal tubule and medullary

[a] Abbreviations: ADH, Antidiuretic hormone or arginine vasopressin (AVP); AII, Angiotensin II; EET, Epoxyelcosatrienoic acid; EGF, Epidermal growth factor; ET-1, Endothelin-1; HETE, Hydroxyeicosatetraenoic acid; IL-1, Interleukin-1; NE, Norepinephrine; NO, Nitric oxide or endothelium-derived relaxing factor (EDRF); PDGF, Platelet-derived growth factor; PGE_2, Prostaglandin E_2; PGI_2, Prostaglandin I_2 or prostacyclin; PGG_2 and PGH_2, Prostaglandins G_2 and H_2, respectively (endoperoxides).

[b] Limited effect on afferent arteriole; virtually no effect on efferent arteriole.

[c] Glomerular capillary tuft arterioles are also affected by the response of the glomerular mesangium.

[d] Mesangium also contains resident macrophages, which can produce vasoactive substances.

[e] (S) antipode has only transient activity.

Compiled using references 19, 27–41.

thick ascending limb, and possibly vasodilation of the medullary capillary plexus (19).

TYPES OF RENAL EFFECTS OF NSAIDs

Because the kidney is the major organ for both concentrating and eliminating xenobiotics such as drugs, its susceptibility to their toxic effects is not surprising. It is somewhat surprising, however, that since most NSAIDs are extensively metabolized (primarily by the liver) to "inactive" metabolites and so little active NSAID is recovered from the urine, NSAIDs nonetheless profoundly affect renal function.

A variety of distinct renal syndromes are produced by NSAIDs. Four types result in renal impairment, namely acute ischemic renal insufficiency, acute interstitial nephritis, analgesic-associated nephropathy, and an unusual syndrome of flank pain and renal failure reported with suprofen use. NSAIDs also affect sodium, potassium, and water homeostasis. Finally, it is possible that increased blood pressure caused by interference of NSAIDs with antihypertensive medications could contribute to progressive renal impairment.

Acute Ischemic Renal Insufficiency

The most common form of NSAID-associated renal impairment is acute renal failure caused by a hemodynamic effect. Disorders, diseases, or drugs that reduce actual or effective circulation cause a homeostatic increase in the production of catecholamines such as norepinephrine and activation of the renin-angiotensin system (1, 2). Within the renal vasculature AII and catecholamine secretion cause vasoconstriction which is counter-regulated by a compensatory release of prostaglandins to maintain adequate renal perfusion (27, 33). In this setting, administration of a NSAID results in a decrease in renal blood flow and glomerular filtration rate, which is often observed after the initial doses of the NSAID and is fully reversible upon discontinuation of NSAID administration (42–44). However, if not recognized early in the course of therapy, prolonged renal ischemia may cause acute tubular necrosis and permanent renal damage (45, 46).

Acute renal insufficiency can also occur in the face of pre-existing chronic renal insufficiency, e.g. patients with creatinine clearances less that 70 ml/min/1.73m^2 (42–44, 47–52). Dehydration, hemorrhage, congestive heart failure, cirrhosis with ascites, and excessive diuresis may also reduce effective circulating volume to the extent that glomerular prostaglandins, particularly PGI_2 and to a lesser extent PGE_2, become operative in the maintenance of renal perfusion (1, 2). In these disorders, PGI_2 and PGE_2 produce vasodilation of afferent glomerular arterioles to maintain glomerular filtration and renal

perfusion in response to increased circulating catecholamines, AII, and vasopressin (33, 34). At the efferent arteriole, preferential vasoconstriction from AII also supports glomerular filtration (38). In this setting, renal impairment manifested by increments in serum creatinine and blood urea nitrogen can occur in patients prescribed NSAIDs.

Acute renal toxicity of NSAIDs has been assessed using two distinct methodologies: acute interventional clinical studies and epidemiologic studies. Acute interventional studies of small groups of preselected subjects demonstrate reductions in creatinine or inulin clearance from 9 to 69% following the administration of NSAIDs (53). Epidemiologic studies, in striking contrast to the findings of acute interventional studies, suggest that the prevalence of renal impairment from NSAIDs is low or that the problem does not exist in all age groups studied (54). In contrast to acute interventional studies that preselect patients at risk, epidemiologic studies using pooled data from pre-marketing clinical trials have often excluded high-risk patients or use insensitive indicators of outcome (55–57).

The seemingly contradictory findings between acute interventional and epidemiologic studies create a dilemma in therapeutic decision-making as it relates to prescribing and the appropriate monitoring of the renal effects of these drugs. Moreover, these results suggest that further investigation of the effects of NSAIDs is needed. We especially believe that additional epidemiologic assessment is needed involving a broader representation of patients, particularly including older patients with multiple clinical conditions of varying severity, and using more sensitive indicators of renal impairment (54).

Our prior interventional studies show that examination of the effect of a NSAID on renal function requires both clearance and balance approaches (42–44). For example, if previously we had only assessed the acute effects of a NSAID using a *clearance* study design, we would have concluded that NSAIDs have a substantial adverse effect on renal function in patients with mild to moderate renal insufficiency and that these drugs should be avoided in all such patients. In contrast, if we had only used a *balance* study design, we would have concluded that NSAIDs have no effects on renal function in these patients. Clearly, neither conclusion would have been correct, hence the necessity for examination of both acute clearance and balance studies (42).

Using these clearance and balance techniques, our laboratory has studied the effects of NSAIDs on renal function in patients with mild to moderate renal insufficiency (creatinine clearance from 19 to 83 ml/min/1.73m^2). Patients were admitted to the Clinical Research Center where they ingested a controlled diet with fixed sodium and potassium intake. Within a week and after attaining sodium balance, a clearance study was performed with administration of the first dose of the NSAID. During this clearance study, control collections were obtained to determine baseline renal function using

inulin and para-aminohippurate as markers of glomerular filtration rate and renal plasma flow, respectively. The first dose of NSAID was then administered, followed by a series of experimental collections to monitor the effect of the drug on renal function. Patients and normal controls were then maintained on the NSAID with daily monitoring of electrolyte excretion, serum electrolytes, and creatinine clearance. This constituted the balance portion of the study. With the last dose of NSAID another clearance study was performed. With this clearance study, control collections were again obtained; these values represent renal function on the background of "chronic" dosing with the NSAID. Experimental collections during this phase represent the effect of a single dose of NSAID superimposed on the background of chronic dosing.

In our studies the effects of a variety of NSAIDs are consistent. In both normal control subjects and patients with renal insufficiency, solute excretion and urinary PGE_2 declined with both the first dose and the last dose. In patients but not in normal subjects, both the first and last doses also caused declines of about 30% in inulin and para-aminohippurate clearances. Hence, in both clearance studies each of the NSAIDs we have studied caused decrements in a variety of renal functional parameters, particularly in the patients with renal insufficiency (42–44).

Figure 3 typifies the results we have observed; it reveals the effects on inulin and creatinine clearance (upper panels) and urinary sodium excretion (lower panel) following a single 50 mg-dose of flurbiprofen to eight patients with chronic renal insufficiency (44). Patients were from 49 to 68 years of age. Seven patients were male. Patients had refrained from taking anti-inflammatory drugs including salicylates-containing products for one month. Seven patients had hypertension but blood pressure was controlled with pharmacotherapy. Both diet and fluid intake were controlled.

Several important points about these time-response profiles are; (*a*) the effect on inulin and creatinine clearance occurred within one hour and the effect was fully reversible within two hours following administration of the dose, and (*b*) the effect on urinary sodium excretion began within one hour and, although the data are not shown, was reversed only after four to five hours of the dose (44). These effects are consistent with the known acute effects of NSAIDs upon the kidney in such patients. (Table 3).

We are interested in whether the repetitive decrements in renal function, though reversible within the dosing interval, could result in a cumulative decrease in renal function. Of interest is the comparison in the clearance studies of baseline renal function (acute study—control) to renal function under the influence of several days to one month of NSAID administration (chronic study—control). For the short-acting NSAIDs we have studied thus far we have found no evidence to indicate an overall decline in renal function

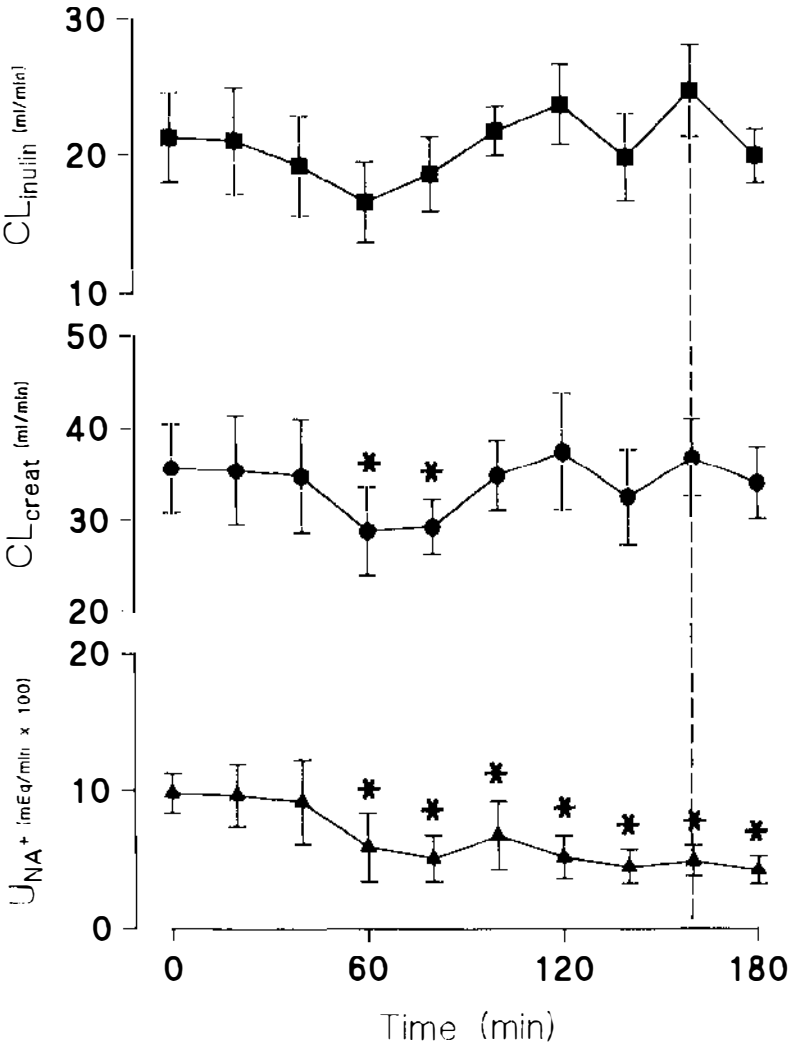

Figure 3 Mean (± s.e. mean) of inulin clearance (top), creatinine clearance (middle), and urinary excretion of sodium (bottom) after a single dose of flurbiprofen 50 mg to patients with chronic renal insufficiency (see text). Time 0 is the baseline value. The vertical dashed line is the mean time of the maximum serum concentration of (S)-flurbiprofen, the enantiomer responsible for prostaglandin inhibition.

* $p < .05$ compared to time 0.

after one month of chronic NSAID therapy (42, 44). We interpret these data to indicate that each single dose of NSAID caused decrements in renal function, but the effects were transient and full recovery to baseline renal function occurred by the end of the dosing interval (42–44).

The overall impact on renal function can be also be addressed by the balance aspect of the study in which the 24-hour creatinine clearance values and electrolyte excretion offer an integrated measure of effect (Figure 4, panels A to D). The eight patients described above received a controlled diet through day 14 and again on days 32 and 33. From these data it is apparent that, compared to the mean control period (MC) flurbiprofen (50 mg four times daily) caused no overall decline in creatinine clearance in patients with chronic

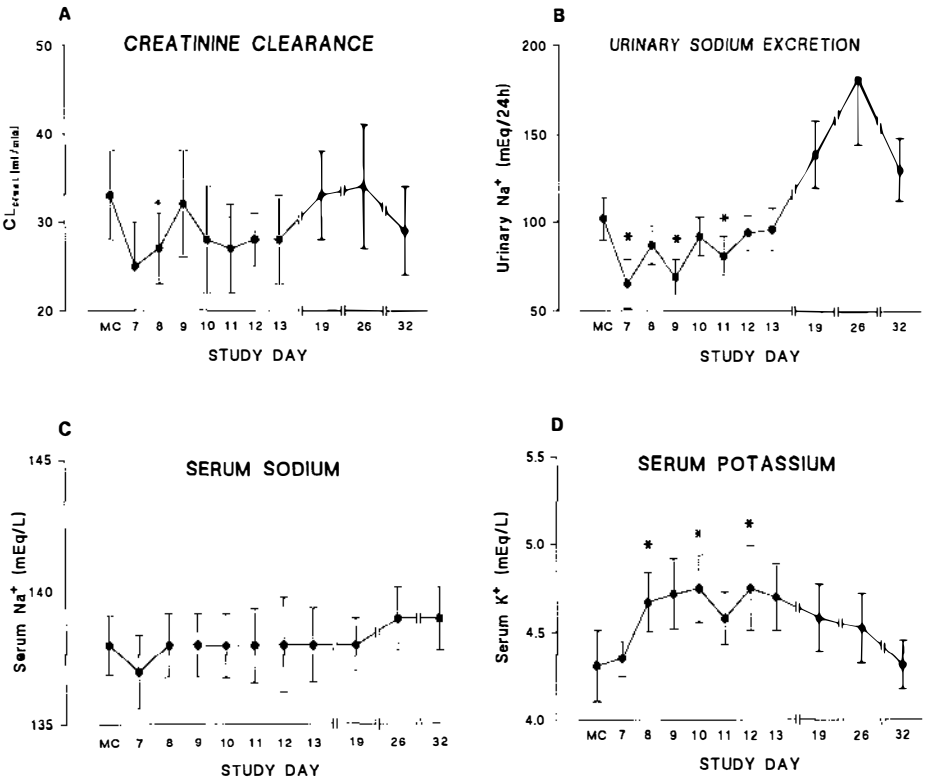

Figure 4 Mean (± s.e. mean) effects of chronic flurbiprofen 50 mg four times daily on daily creatinine clearance (panel A), urinary sodium excretion (panel B), and serum sodium (panel C), and potassium (panel D) concentrations. MC is the mean result of measurements made on days 4 and 5, immediately before the patient's first dose.

* $p<.05$ compared to MC.

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renal insufficiency (Figure 4, panel A). Thus, the cumulative effect of the individual doses was not sufficient to cause an overall adverse effect on renal function. In contrast, urinary excretion of sodium remained decreased compared to the control period (Figure 4, panel B). Urinary sodium excretion increased above baseline after study day 13 when the controlled study diet was discontinued. Though the effect upon urinary sodium excretion was profound, serum sodium concentration was stable (Figure 4, panel C). Serum potassium increased on average by 0.44 mEq/liter beginning within one week of the first dose, but returned to mean control values despite repeated administration of flurbiprofen (Figure 4, panel D). These effects are consistent with the known effects of chronic NSAID administration upon the kidney and systemic vasculature (Table 3).

We also examined the effects of flurbiprofen on patient weight and blood pressure (Figure 5, panels A to C). There were few overall effects on these parameters while patients received the controlled diet. However, when patients received their normal diets, average increases of 2.8 kg in weight, and 27 mm Hg and 12 mm Hg in systolic and diastolic blood pressure were observed.

An obvious question is whether a longer-acting NSAID such as piroxicam might result in an overall adverse effect. Additional questions are whether a different putative risk group such as the elderly would demonstrate similar or different responses to a short-acting NSAID compared to our previous studies in patients with renal insufficiency, or whether an adverse effect would only occur in elderly patients with chronic disease and diminished baseline renal function. These findings also raise the obvious question as to the potential effects of a NSAID from a different class. Can a patient who has an acute decrement in renal function with one NSAID be safely treated with another?

Figure 6 addresses this last question in a single patient; it shows the results of acute inulin clearance studies in a 73 year-old patient with osteoarthritis, hypertension, chronic renal insufficiency, and atherosclerosis, who is unable to tolerate any NSAID as documented by the dramatic effect of all three NSAIDS tested on his renal function. This patient's inulin clearance decreased by 65%, 79%, and 64% with sulindac, piroxicam, and ibuprofen, respectively. These NSAIDs were administered separately at least one month apart. Discontinuation of all three NSAIDs was required within four days because this decrease in renal function was sustained. Thus, patients who are susceptible to the acute hemodynamic effects of NSAIDs must have their renal function carefully monitored for the onset of renal insufficiency whenever any NSAID is administered.

The results in this patient lead, in turn, to the issue of the putative renal-sparing effect of sulindac (58–60). Sulindac is a NSAID structurally and pharmacologically related to indomethacin. In order for sulindac to exert

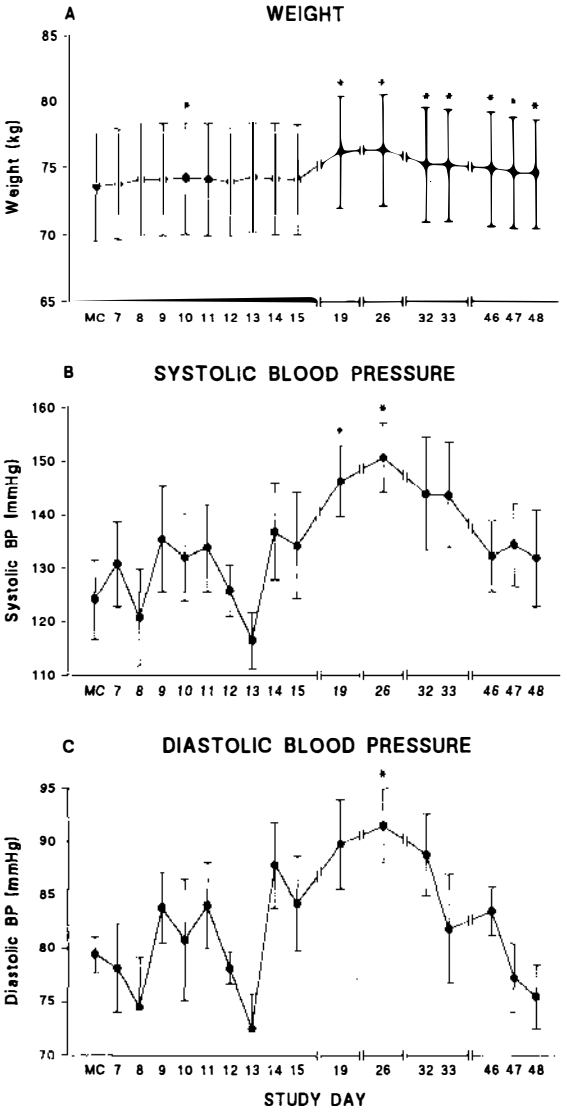

Figure 5 Mean (± s.e. mean) effects of chronic flurbiprofen 50 mg four times daily on patient weight (panel A), and systolic (panel B) and diastolic (panel C) blood pressures. MC is the mean result of measurements made on days 4 and 5, immediately before the patient's first dose.

* $p<.05$ compared to MC.

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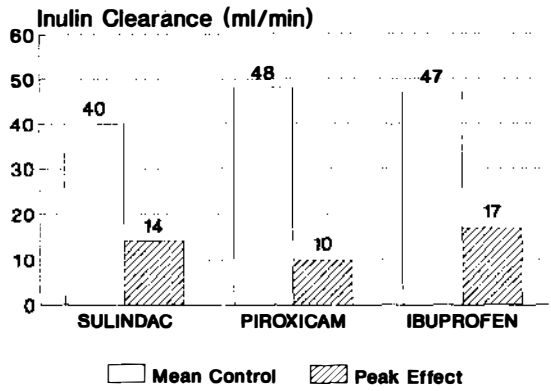

Figure 6 Effect of a single doses of sulindac 200 mg, piroxicam 20 mg, and ibuprofen 800 mg on inulin clearance in a patient susceptible to the renal effects of NSAIDs (see text). Each administration of NSAID was separated by at least one month. Mean control represents the patients baseline measurements, immediately prior to NSAID administration. Peak effect is the nadir response achieved within three hours of dosing.

pharmacologic activity, it must be reduced from its inactive pro-drug, sulindac sulfoxide, to its active metabolite, sulindac sulfide (61). Although sulindac is comparable to other NSAIDs with respect to pharmacologic effect, it has been suggested that it is less likely to inhibit renal prostaglandins since the kidney is able to enzymatically convert the active sulfide back to the inactive sulfoxide (65, 67). Sulindac might therefore cause less renal toxicity (48, 62–64). As such, it is advocated by some for preferential use in patients susceptible to adverse renal effects of other NSAIDs such as the elderly (63, 64). There currently is considerable debate concerning the renal sparing effect of sulindac. For example, in a study by Ciabattonni et al (48), ten female patients with chronic glomerular disease received sulindac 400 mg per day for one week, with no significant reduction in renal function or renal prostaglandin synthesis. In addition, in a report by Bunning and Barth (62) on three patients who experienced reversible azotemia with naproxen or ibuprofen were able to tolerate therapy with sulindac. On the other hand, our own studies (58–60), and those of others (47, 66–72), offer conflicting data. All concluded that sulindac had similar renal effects as other NSAIDs.

We have examined the effects of sulindac on renal function using three paradigms of increased sensitivity of renal function to NSAIDs: (*a*) sodium depleted normal volunteers also stressed with furosemide (58); (*b*) dogs which have undergone controlled hemorrhage (59); and (*c*) patients with severe alcoholic cirrhosis (60). Our interpretation of these data is that sulindac

represents a less potent NSAID in the doses used clinically, but that it can affect renal prostaglandins and thereby adversely affect prostaglandin-dependent renal functional parameters in susceptible patients.

Acute Interstitial Nephritis

Interstitial nephritis is a rare but severe form of NSAID nephrotoxicity. It has been estimated to occur in one of every 5,000 to 10,000 patients and differs from acute ischemic renal insufficiency in onset, severity, and duration (1). Although interstitial nephritis can occur within one week of NSAID administration, it usually occurs following several months to one year after the start of NSAID administration (73). Typically, patients present with greatly elevated serum creatinine (often exceeding 6 mg/dl), and edema, and nephrotic-range proteinuria occurs in two thirds of patients (urinary protein > 3.5 g/24h). Temporary dialysis may be necessary. Histological findings from renal biopsy specimens demonstrate diffuse interstitial edema with evidence of mild to moderate inflammation, and cellular infiltration of predominantly cytotoxic T cells with smaller numbers of B cells and eosinophils (74, 75). Eosinophiluria, eosinophilia, fever, and skin rash are mostly absent, in contrast to acute interstitial nephritis caused by beta-lactam antibiotics such as methicillin. Morphological evidence of glomerular involvement, such as fusion of foot processes of the vessels within the glomerular capillary tuft, is present in 86% of cases (76). Although glomerulosclerosis and arteriosclerosis are often noted, many of the patients experiencing NSAID-associated interstitial nephritis are elderly persons, rendering these findings nonspecific. The disease also occurs in children who are receiving NSAIDs for the treatment of juvenile rheumatoid arthritis. Though corticosteroids have been used to treat patients with interstitial nephritis, its therapeutic benefit is questionable. Most patients respond to discontinuation of the offending NSAID within 1 to 3 months (73, 77).

Other than duration of use, risk factors for the development of this syndrome are not known. However, fenoprofen was implicated in 20 of 43 cases (46%) of NSAID-associated interstitial nephritis in a recent case series review (73). Although NSAIDs from all of the other chemical classes have been implicated, the high prevalence of those cases associated with fenoprofen is much greater considering its limited use. It is noteworthy that a recent study demonstrated that fenoprofen acyl-glucuronide is capable of forming reactive metabolites by acyl-glucuronide migration, irreversibly binding to albumin in a stereoselective fashion (24). Conceivably, if the macromolecular albumin-NSAID complex is transported into the glomerular mesangium, glomerular integrity could be disrupted from the release of cytokines, interleukins, and other substances found within the mesangium. Similarly, the NSAID-protein

adduct could possess adverse immunologic properties by increasing interleukin production or stimulating either resident macrophages or cytotoxic T lymphocytes that may then be responsible for fenoprofen-associated interstitial nephritis (78). Interestingly, zomepirac and tolmetin, NSAIDs also known to cause a wide variety of immune reactions, are also capable of forming reactive metabolites that irreversibly bind to albumin (25, 26).

Analgesic-associated Nephropathy

The most severe and often irreversible form of renal toxicity caused by NSAIDs is analgesic-associated nephropathy. The use of the terminology "associated" is stressed because the cause of this form of renal toxicity from NSAIDs remains unknown and its linkage to NSAIDs in general is circumstantial. Spühler and Zollinger first recognized renal papillary damage among Swiss watch factory workers who used analgesic products (79). They observed necrosis of the papilla in 20 of 32 patients and believed that it had occurred *secondary* to chronic interstitial nephritis caused by abuse of a combination analgesic product called Saridon®, containing propyphenazone, phenacetin, and caffeine. It is now known that papillary necrosis is the *primary* lesion from which chronic interstitial nephritis evolves (80).

Patients with analgesic-associated nephropathy typically share a common history of continuous analgesic abuse over many years (81–83). Often a variety of analgesic compounds have been abused: these include products containing combinations of analgesics (aspirin and phenacetin) and the analgesic adjunct, caffeine. Phenacetin was initially implicated as the causative agent in combination analgesic products such as Vincent's and Bex powders and was therefore referred to as "phenacetin kidney" (82, 87). However, all of the ingredients of these analgesic mixtures have been, at one time or another, reported as the causal agents (88, 89). Consequently, the cause of analgesic-associated nephropathy continues to be a source of controversy spanning four decades.

Early on, it became apparent that analgesic-associated nephropathy was a major problem particularly in Australia and in some European countries (81–83). The prevalence of the disorder demonstrated wide geographic variation both within and between countries (81). Surveys have shown that the percentage of patients who present with end-stage renal disease associated with analgesic abuse are highest for Belgium (36%), South Africa (22%), Australia (4 to 22%), Denmark (0.2 to 2.8%), Switzerland (0.76 to 1.75%), and New Zealand (1.6%); they are lowest in England (0.07 to 0.41%), Scotland (0.6%), and the United States (0.23% to 10%) (83–86).

Much of the evidence suggesting an association between NSAIDs and analgesic nephropathy derives from autopsy reports, case reports and case

series, and ecologic studies. Such studies have been critical to better definition of the problem and in the evolution of our understanding of its extent and distribution, yet have also clouded our understanding of these same areas through imprecision and bias. Many case reports and series have been reported by nephrologists who dialyze and treat patients with analgesic-associated nephropathy in their routine practices. But prevalence estimates from such environments that have a high concentration of cases because of referral of patients from general practitioners cannot be extrapolated to the general population. Earlier studies have been reviewed in great detail in four previous monographs (for review see 81–83, 87). Most studies in the United States suggest that the prevalence of analgesic-associated nephropathy is low (81, 83) with the exception of one study in North Carolina for which the prevalence was 10% (86). One of the few controlled epidemiologic studies was a case-control study to assess the relationship between analgesic use and end-stage renal disease in 527 patients and 1047 matched control subjects from the northeastern United States (90). The study failed to demonstrate a statistically significant risk of end-stage renal disease for analgesics used alone or in combination. The authors reasoned that either the risk of end-stage renal disease from analgesics was low in the geographic area of assessment or the overall risk was low. However, long-term, high-dose use of these drugs may not have been common in this study population. Notwithstanding the negative results of this study, a considerable volume of data has accrued from experimental and nonexperimental studies from Australia and Europe, with findings suggestive of an endemic distribution of cases.

In 1968, Dubach and colleagues initiated a prospective, controlled cohort study in a northwestern industrial area of Switzerland to study the incidence of renal disease associated with the abuse of analgesics (91). This region of Switzerland is marked by high use of analgesics and the source of the original reports of Spühler & Zollinger. Morbidity from analgesic-associated nephropathy in this area has been high; 40% of patients receiving dialysis had analgesic-associated nephropathy. They identified 623 Swiss women 30 to 49 years of age who were thought to be regular users of phenacetin, as evidenced by the presence of acetaminophen (paracetamol) in their urine; they also identified 621 controls (91). Both groups had normal renal function at baseline. By 1975, 216 women in a high-analgesic use group, 231 in a low-use group, and 506 women in the control group were available for analysis. Urinary concentrating ability (papillary necrosis results in loss of the ability to form concentrated urine) and serum creatinine were measured, as was the presence of acetaminophen. In the high-use group, 4.6% of the women had a loss of urinary concentrating ability compared to 1.3% in the low use, and 1.0% of the controls. Increases in serum creatinine persisted in 5.3% of the

high-use group, compared to 0.4%, and none in the low-use and control groups, respectively. None of the subjects in any of the groups had significant hematuria or proteinuria (in contrast to the nephrotic-range proteinuria seen with acute interstitial nephritis from NSAIDs).

At eleven years of follow-up, urinary concentrating ability was impaired in 23.3% of the high-use group compared to 6.7% of controls; serum creatinine was increased in 6.7% of the high-use group, and 0.9% of controls (89). Also at 11 years, 39 persons (6.7%) had died in the study group, primarily due to renal and cardiovascular causes, compared to 13 (2.3%) in the control group. Twenty-year mortality (in 89% of the original cohort members) revealed a relative risk of death for any reason of 2.2 among the high-use group and 16.1 for renal and urogenital causes (93).

The findings of these longitudinal studies are consistent with the high risk of morbidity suspected from the results of autopsy reports and case series within northwestern Switzerland. Although the authors implicate phenacetin as the causative agent, acetaminophen was actually measured in the urine of patients. As such, evidence for the role of phenacetin in these studies was indirect. It is unclear whether routine patient reports of analgesic intake were used to confirm use of phenacetin or acetaminophen. Acetaminophen has been implicated in one case-control study that was subsequently criticized because the analgesic consumption of a large proportion of the cases was established using proxy reports from case relatives (94).

Experimental studies in animals have failed to support the hypothesis that phenacetin causes analgesic-associated nephropathy (81, 95). Rats have been studied most but have major differences that make extrapolation of the results to humans difficult (96). The rat kidney has a single papilla and more long nephrons than the human kidney. The blood supply within the rat kidney is more restrictive, which may impede protection of the papilla from anoxic insult. Gunn rats appear to be particularly sensitive to papillary necrosis. Studies in rats have demonstrated that papillary necrosis occurs following phenacetin administration only with extraordinarily large doses. In contrast, papillary necrosis readily occurs in animals given aspirin or acetaminophen, both alone and in combination. This was also the case with concurrent administration of aspirin or acetaminophen with phenacetin or caffeine. From an extensive review of such experimental studies, Prescott has concluded that the anti-inflammatory ingredient in analgesic combinations is the causative agent (81). However, this is not supported by the most recent study by Dubach et al (93).

Finally, ecologic studies have demonstrated no reduction in the prevalence of analgesic-associated nephropathy following the removal or regulation of phenacetin distribution (81–84). Although analgesic-associated nephropathy

has been reported with a variety of the newer NSAIDs, such reports have been sparse (81–84, 97, 98), despite their availability for about 20 years and near ubiquitous use.

Characteristics of patients with analgesic-associated nephropathy have been determined. Patients are often females within the ages of 40 to 50 years. Males may present later in the course of the disease with more severe renal insufficiency and hypertension (99). Interestingly, most patients abuse the analgesic mixtures for their mood-elevating effects or to give them a lift (82, 85). In the endemic areas of Switzerland and Australia combination analgesic mixtures were readily accessible from vending machines within factories. In some, the drugs were available without charge. Moreover, the caffeine content of these products may have played a role in their continuous use by creating a headache in those who discontinue them. Hence, use of these products may have been increased by a composite of ready availability, low or no cost, and a physiologic reminder to continue the drug product.

Patients with analgesic-associated nephropathy often present with a variety of problems (81). Patients may have hypertension, gastrointestinal ulceration, urinary tract infection, somatic complaints such as chronic headaches, depression, and often, cardiovascular disease. Anuria may develop from obstruction caused by sloughed papillae. Proteinuria is rarely seen in analgesic-associated nephropathy, distinguishing it from acute interstitial nephritis seen with NSAIDs. Many patients present with end-stage renal disease and hypertension. For such patients, the outlook is grim. The five-year survival was estimated to be 44% in 55 patients (100). In another study, 57 patients were followed for up to five years with 29 deaths (51%) and 56% developed progressive renal insufficiency (101). Although those with milder disease may slowly regain lost function, many continue to use analgesics and suffer progressive decrements in renal function eventuating in end-stage renal disease and the need for chronic dialysis or kidney transplantation (81, 83). Still others may be prescribed newer, supposedly safer NSAIDs and suffer progressive deterioration of renal function.

The pathology of analgesic-associated nephropathy has been established primarily from animal models. The initiating lesion begins within the papillae and ascends into the cortex as the disease progresses. Papillae of both kidneys are usually afflicted (102). Three stages of development have been described based on severity (103). The *early stage* involves changes within the inner medulla with necrosis of the medullary loops of Henle and medullary capillaries. The *intermediate stage* involves evidence of necrosis throughout the papillae. In the *advanced stage* the papilla is destroyed. In this terminal stage, the papilla may show evidence of separation or may be entirely absent. A border of calcification is sometimes seen proximal to the advancing edge

of necrosis. Examination of the cortex in the advanced stage may reveal interstitial fibrosis, infiltration of a variety of inflammatory cells, and tubular atrophy. Radiological examination reveals shrunken kidneys with irregular borders (104).

The time course of the development of analgesic-associated nephropathy is not known. However, studies in animals, which may be particularly sensitive to papillary necrosis, have demonstrated changes in the papilla beginning as early as two weeks following aspirin administration (105). Most patients with analgesic-associated nephropathy have taken these drugs for many years at high dosages. Cumulative dosage usually exceeds several kilograms of drug. One estimate suggested that 73% of persons ingesting a cumulative dose of 4 kg of phenacetin will suffer renal impairment and 37% will die as a result of complications resulting from papillary necrosis (81).

The mechanism of papillary necrosis from NSAIDs is unknown. Duggin has suggested the importance of the presence of at least one of two factors for its development (95). First, the tissue must possess a metabolic or functional predisposition such as susceptibility to ischemia from reduced renal blood flow. As described previously, NSAIDs may cause renal ischemia and it has been postulated that the mechanism for papillary injury could be the result of a prostaglandin-mediated, acute ischemic insult. Long-term inhibition of vasodilatory autacoids (Table 3) could theoretically lead to prolonged papillary ischemia followed by necrosis. Several studies have demonstrated involvement of the vascular bundles in the outer medulla following NSAID administration to rats (80, 105). Increased perivascular collagen may contribute to narrowing and eventual destruction of vasa recta that nourish the medullary interstitium. Finally, analgesic-associated nephropathy in rats occurs with a variety of NSAIDs, thereby indirectly supporting an ischemic mechanism.

The second requisite Duggin proposed was that the drug must selectively concentrate in the papillae (95). Although aspirin and acetaminophen selectively distribute to the medulla, phenacetin does not. However, the major metabolite of phenacetin is acetaminophen, which accumulates within the papillae (95). Accumulation of NSAIDs in animal renal tissue has been demonstrated for a variety of NSAIDs, but studies do not specify whether there were differences among tissue compartments such as the papillae (21–23).

Direct toxic effects of NSAIDs or reactive metabolites could also occur, as has been described with acetaminophen overdosage. Distribution, transport, or binding of these reactive metabolites could depend on such factors as volume depletion, urinary pH, or the presence of other analgesics. Dehydration has been repeatedly mentioned as a risk factor for papillary necrosis (95,

96). Mechanistically, dehydration may render the medullary blood flow prostaglandin-dependent and increase the medullary concentration of the offending NSAID (96).

It is entirely possible that more than one mechanism is important in the evolution of papillary necrosis (96, 103). With repeated administration of a NSAID, toxicity could be initiated from a chronic hemodynamic effect resulting in cumulative ischemia. Altered metabolism of the NSAID with formation of reactive metabolites within the ischemic region could then lead to progressive tissue destruction (81, 106). Interaction between ingredients could also occur. For example, salicylate may deplete renal glutathione thereby making the kidney more susceptible to the toxic effects of acetaminophen (95).

In summary, based on many reports that have appeared over the past forty years, it is apparent that papillary necrosis is associated with the use of NSAIDs, particularly analgesic mixtures containing aspirin, phenacetin, and caffeine. Less apparent is which of these ingredients, alone or in combination, are responsible for the development of analgesic-associated nephropathy and data are conflicting. The longitudinal study of Dubach and colleagues suggests that phenacetin or a metabolite such as acetaminophen are causal (91–93). In contrast, evidence assembled by Prescott suggests that both phenacetin and its major metabolite, acetaminophen, play a minor role in the development of this disorder, but that the anti-inflammatory component (e.g. salicylate) is nephrotoxic (75). Recent reports indicate that analgesic-associated nephropathy may occur with a variety of newer NSAIDs as well, but the number of reports has been small, particularly in relation to the number of patients receiving modern NSAIDs.

SUMMARY

NSAIDs pose little threat of renal insult in normal, healthy persons at therapeutic dosages. However, NSAID administration to susceptible persons may cause decrements in renal plasma flow and glomerular filtration rate within hours. Such acute noxious renal effects are mediated by products of arachidonic acid metabolism. Precipitous decrements in glomerular filtration and renal ischemia, manifested by increased serum creatinine and urea nitrogen, are possible. However, these effects are usually fully reversible with prompt discontinuation of the offending NSAID. Risk factors for the development of these acute renal effects are known.

Acute interstitial nephritis with or without nephrotic syndrome is a rare form of renal toxicity that typically occurs between 2–18 months of use. Renal impairment may be so severe as to require temporary hemodialysis; however, renal function usually returns to normal upon discontinuation of the NSAID.

The mechanism of acute interstitial nephritis is presumed to be of allergic origin but could also be caused by a reactive metabolite. Fenoprofen use appears to be associated with a much higher risk for its development.

In contrast to the acute effects of NSAIDs, irreversible, analgesic-associated nephropathy manifested by papillary necrosis and chronic interstitial nephritis may occur following months to years of high doses of analgesic mixtures. The mechanism by which combination analgesics produce this form of renal injury is unknown and could be either a result of medullary ischemia or a direct effect of a reactive metabolite.

An important issue to be resolved is the relationship between the acute, reversible, prostaglandin-mediated renal effects of the NSAIDs and chronic, irreversible destruction, if such a relationship exists. Theoretically, continual or repeated decrements in renal function in patients with predisposing risk factors could cause or contribute to progressive deterioration in renal function. Elevations in blood pressure or interference with the effects of antihypertensive medications could theoretically also contribute to long-term renal deterioration.

In addition to renal syndromes caused by NSAIDs that result in renal impairment, other transient effects on electrolyte and water metabolism may also occur. Reduced secretion of sodium may result in formation of edema, exacerbation of heart failure, or increased blood pressure. Hyporeninemic-hypoaldosteronism may produce hyperkalemia. Finally, reduced excretion of water has rarely caused hyponatremia.

It has been suggested that NSAIDs may be renoprotective in patients with nephrotic syndrome (107). Others have suggested that sulindac is "renal-sparing" because of a unique metabolic pathway that supposedly limits the exposure of the kidney to the active sulfide metabolite (48, 62–64). The detrimental effects on renal function for the patient presented in Figure 6 are not dependent on the appearance of sulindac sulfide in the urine. Instead, this effect is presumably caused by the hemodynamic effect of active drug as it traverses the glomerular vasculature. Because of such conflicting information, clinicians and patients alike are uncertain about the use of these drugs and fear renal impairment from their use. These conflicting data have also left the clinician in a quandary about the safest NSAID to prescribe for patients with diseases that predispose them to renal toxicity. This creates a major dilemma: on one hand, NSAIDs have an established record of versatility in the palliative treatment of a wide variety of painful disorders with a wide margin of safety compared to alternative therapy such as opiate derivatives; on the other is their potential for renal toxicity. Since the mechanisms for the commonest forms of acute nephrotoxicity are understood, patients at risk can be prospectively defined. These patients can in turn benefit from closer monitoring of renal function when a NSAID is started. The therapeutic margin of these drugs can thereby be enhanced.

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