Glomerular, tubular and interstitial nephritis associated with non-steroidal antiinflammatory drugs. Evidence of a common mechanism

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Aims To study the mechanisms behind NSAID-associated nephropathy.
Methods Analysis of published case reports satisfying strict criteria for NSAID nephropathy.
Results Ninety-seven cases with acute nephritis (AN; 19 patients), minimal change nephropathy (MC; 38 patients), membranous glomerulonephritis (MGN; 19 patients), focal sclerosis (FS; 13 patients) and other glomerulonephritis subgroups (8 patients) were identified. Hypersensitivity reactions were seen in all groups, most often in AN. Proteinuria was more severe in MC and FS than in MGN and unrelated to amount of glomerular deposits. The mean NSAID treatment time was 1.7 months in AN, 8.2 months in MC and 39 months in MGN and associated with amount of glomerular deposits, fusion of podocytes and proteinuria, and inversely associated with hypersensitivity, interstitial damage and renal failure. Rheumatic diseases were common in MGN. At follow-up 68 of 72 patients who had discontinued NSAID treatment had improved, 57 with normal renal function.
Conclusions NSAID nephropathy may be caused by hypersensitivity. The reaction is milder than in drug-induced acute tubulointerstitial nephritis, probably because the offending drug inhibits the inflammatory reaction it has started itself. Heavy proteinuria is probably due to lymphokines produced as a result of the immunological response. If the allergic reaction is strong, AN is produced rapidly with severe renal failure but little proteinuria; if it is less violent, immunocompetent cells may develop to produce lymphokines and proteinuria. Immune complexes may be formed eventually, secondary to the increased glomerular permeability, more easily in patients with a hyperactive immune system and with little consequence for renal function.

Keywords: non-steroidal antiinflammatory drugs, NSAID nephropathy, tubulointerstitial nephritis, glomerulonephritis, minimal change nephropathy, membranous glomerulonephritis, nephrotic syndrome, side effects

Introduction

Treatment with non-steroidal anti-inflammatory drugs (NSAID) may produce renal side effects. The most common are renal failure with disturbances of salt and water metabolism because NSAIDs inhibit the synthesis of prostaglandins involved in the intrinsic autoregulation of renal function. The effects on renal function are almost always seen in patients with preexisting renal disease or with decreased renal perfusion because NSAIDs have no influence on normal renal function [1–5].

In patients with normal kidneys NSAID treatment may trigger a spectrum of nephritides including tubular, interstitial or tubulointerstitial nephritis, chronic interstitial nephritis with papillary necrosis, and tubulointerstitial nephritis combined with the nephrotic syndrome, often followed by acute or chonic renal failure. In addition, the patients who present with the nephrotic syndrome may have a variety of glomerular changes indistinguishable from those found in minimal change nephropathy, membranous glomerulonephritis, focal sclerosis and other glomerulonephritic subgroups [2, 3, 6–8].

The mechanisms for these nephritides (NSAID nephropathy) have not been explained satisfactorily. Most authors consider that each of them is a separate entity with its own cause and mechanisms. A striking finding in NSAID nephropathy, however, is the absence of a clearcut demarcation between the various subgroups; very often, findings typical for tubular nephritis, interstitial nephritis

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and glomerulonephritis are found in the same patient. Considering the widespread use of NSAIDs, NSAID nephropathy is a rare complication. It seems highly unlikely that patients with such a rare disease should suffer from two or three rare renal diseases at the same time, each with a different cause. A more likely explanation is that these nephritides have a common cause and that the pathogenetic processes are modulated by secondary factors that may vary from patient to patient. The present review was performed to see if the findings in the major subgroups of NSAID nephropathy were compatible with this assumption.

Methods

To isolate the renal effects of NSAID from other pathogenic conditions the following criteria for inclusion of a case report were used: renal disease should have occurred during treatment with NSAID; treatment with other nephritogenic drugs should have been discontinued at least 3 months before admission; the patient should not suffer from an underlying renal disease; or from diabetes, gout, systemic lupus erythematosus (SLE) or another disease known to predispose to renal disease unless an investigation prior to NSAID treatment, or after its discontinuation, had shown normal urine and normal renal function; the renal tissue should have been studied microscopically, and serum creatinine or creatinine clearance, and degree of proteinuria should be given.

Case reports written in English, German or French were sought in the MEDLINE database using the following search term: (non-steroidal antiinflammatory OR the generic name of each of the NSAIDs in clinical use) AND (nephropathy OR interstitial nephritis OR tubular nephritis OR glomerulonephritis OR glomerulopathy OR nephrotic syndrome OR acute renal failure). Case reports were also sought in reviews of acute renal failure, acute interstitial and tubulointerstitial nephritis and by reviewing the references of the case reports.

The following information was extracted from the case reports: Age and sex, the indication for and the length of NSAID treatment, information about other medical treatments, the peak urinary protein and serum creatinine, the blood pressure, the urine sediment, any symptoms or laboratory data indicating a hypersensitivity reaction, the renal biopsy findings, and glomerular function and degree of proteinuria at follow-up.

Unpublished biopsy findings were sought from the authors of the more recent reports.

Statistics

As almost all data were dichotomous it was necessary to use non-parametric statistics. For each parameter the patients were divided into two or three appropriate groups as described in Results. Associations between groups were calculated by chi-square using Fisher's exact test when crosstabs included four squares only and linear-by-linear association when crosstabs included more than four squares. The SPSS statistical program was used for the calculations; P was two-tailed.

Results

Clinical and laboratory findings

Ninety-seven case reports that fulfilled the selected criteria were identified [9–73] with a male/female ratio of 34/63, mean age 54.0 years (median 57). The indication for NSAID treatment was a musculoskeletal disorder in 52 patients, a rheumatic disorder in 30, miscellaneous disorders in eight and unknown in seven. Nineteen different NSAIDs were used; most often fenoprofen which was used in 23 patients, followed by sulindac (eight patients), ibuprofen and diclofenac (seven patients each). Thirteen patients had been treated with more than one NSAID, in most cases the other NSAID was aspirin. The total treatment time was given for 91 patients and varied between 24 h and 22 years (median 6 months) (Table 1). Thirty-three patients had other medical treatments. Blood pressure at admission was given for 67 patients and signs or symptoms of hypersensitivity was noted in 32 patients (Table 2). The glomerular function was determined in 63 patients by serum creatinine, in 19 by creatinine clearance and 15 had dialysis. Degree of proteinuria was quantified in 88 patients, in nine it was graded by albustix only (Table 1). A urine sediment was studied in 78 patients.

Biopsy findings

The renal biopsy was studied by light microscopy (LM) in all patients, by immunofluorescence microscopy (IM) in 75 patients, and by electron microscopy (EM) in 64 patients.

Light microscopy In 67 patients the glomeruli were normal. Nineteen of these patients had minimal proteinuria (<1 g 24 h^{-1}; median 0.4 g 24 h^{-1}); all except two had varying degrees of interstitial or tubulointerstitial damage, all had renal failure and a short treatment time (median 1 month). These nineteen patients were classified as acute nephritis (AN). Thirty-seven of the patients with normal glomeruli had nephrotic range proteinuria and no deposits by IM and/or EM and were therefore classified as minimal change nephropathy (MC). Nine of the patients with normal glomeruli by light microscopy had evidence of membranous glomerulonephritis (MGN) on immunofluorescence and/or electron microscopy and were

Table 1 Grouping of the patients according to various parameters.

Parameter	*Group 1*	*Group 2*	*Group 3*	*Group 4*	*No or deficient data*
Treatment time	24 h–3 months	4–11 months	>11 months		
n	36	27	28		6
Blood pressure	Diastolic <95 mmHg	Elevated			
n	46	21			30
Glomerular function	Normal	Reduced	On dialysis		
n	20	62	15		0
Proteinuria	0–1.3 g 24 h^{-1}	2.3–8.5 g 24 h^{-1}	8.5–35 g 24 h^{-1}		
n	25	33	33		6
Glomerular deposits*	None	A few	Many		
n	49	20	15		13
Fusion of podocytes	None	Partial	Diffuse		
n	4	8	42		43
Tubular changes	None	Mild or focal	Severe		
n	24	23	24		26
Interstitial changes	None	Mild or focal	Severe		
n	17	23	54		3
Interstitial cells	None	A few	Many		
n	22	23	45		7
Hypersensitivity	No evidence	1 symptom	2 symptoms	3 symptoms	
n	20	21	9	2	45
GFR at follow-up	Normal	Improved	Worsened		
n	58	11	4		24

*According to the combined results from IFM and EM.

Table 2 Number of patients with signs or symptoms of systemic hypersensitivity.

	Yes	*No*	*No information*
Eosinophilia (>300/mm^3)	16	42	39
Eosinophiluria	2	52	43
Many interstitial eosinophils	13	75	9
Rash	7	90*	
Fever	7	90*	
Any evidence of hypersensitivity	32	20	45

*No information was considered as absence.

Table 3 Number of patients by type of nephritis.

Acute nephritis	19
Minimal change disease	38
Membranous glomerulonephritis	19
Focal sclerosis	13
Anti-GBM nephritis	2
Focal, proliferative glomerulonephritis	5
Unclassifiable	1
Total	97

grouped together with ten patients with typical MGN on light microscopy. Twelve patients with 10 or more % sclerotic glomeruli and normal non-sclerotic glomeruli by LM and one patient with glomerular tip lesion were classified as focal sclerosis. Eight patients had other types of glomerular changes (Table 3).

Immunofluorescence microscopy (IFM). IFM was performed in 71 cases, immunoperoxidase microscopy in one. In 34 patients no deposits were seen. Twenty-one had granular deposits with various localizations in the glomeruli; four had also tubular, interstitial or vascular deposits. Ten patients had tubular, interstitial or vascular deposits but no glomerular deposits, two had linear glomerular deposits.

Electron microscopy This was performed in 63 patients. In 19 patients deposits were noted in the glomeruli; 12 had subepithelial and/or intramembranous deposits, three had subendothelial deposits, nine had mesangial deposits and 33 had none. The condition of the foot processes of the glomerular epithelial cells were recorded in 54 patients (Table 1).

Follow-up

The glomerular function at follow-up, a few days to 10 years after discontinuation of NSAID (median 4 months),

was reported in 86 patients. Patients with an abnormal glomerular filtration rate (GFR) and followed for less than 1 month or whose follow-up time was unknown, and patients with insufficient information about possible NSAID treatment during follow-up were excluded from the statistical calculations. Four patients, who had continued taking NSAID, were also excluded. In one GFR had worsened; the other three were on dialysis treatment. Most of the rest had recovered completely and even those whose GFR was still abnormal at follow-up had improved considerably. Four patients had worsened, three of them had had severe renal failure at admission (Table 1).

Associations

Associations between all parameters in Table 1 and the major subgroups were calculated, as were associations between each parameter. In the following the most important associations are mentioned only.

The lowest GFR was seen in patients with AN (AN *vs* all others; $P<0.01$). The GFR was also lower in patients with MC than in patients with MGN ($P<0.01$). A strong, positive correlation was found between amount of glomerular deposits and the GFR ($P<0.00001$). Except for MGN, interstitial damage was frequent in all groups and associated with a low GFR ($P<0.0001$). Similar findings were noted for tubular damage.

As a consequence of the criteria chosen for AN, degree of proteinuria was less severe in AN than in MC and MGN. Proteinuria was associated with foot process fusion ($P<0.001$). Less predictable was that proteinuria was more pronounced in MC and FS than in MGN ($P<0.05$). No association was found to number of glomerular deposits.

Treatment time was strongly associated with diagnoses. Almost all cases of AN occurred during the first 3 months of treatment ($P<0.0001$; AN *vs* all others) whereas most patients with MGN had been treated for more than 11 months ($P<0.01$; MGN *vs* all others). The mean treatment time for AN was 1.7 months (median 1 month; range 24 h to 3 months); for MC it was 8.2 months (median 6 months; range a few days to 24 months) and for MGN it was 39.0 months (median 12 months; range 5 weeks to 22 years). Treatment time was also associated with glomerular deposits ($P=0.01$), proteinuria ($P<0.02$) and foot process fusion ($P<0.001$), and inversely associated with interstitial damage and hypersensitivity ($P<0.02$ in both cases). Signs or symptoms of hypersensitivity occurred in all types of nephritis, but most often in AN ($P=0.01$; AN *vs* all others). Patients with MGN and patients with glomerular deposits had more often a rheumatic disease than had other patients ($P<0.02$ in both calculations). No associations were found with sediment findings, use of diuretics or antihypertensive drugs, or with blood pressure.

Patients who had been treated with more than one NSAID had more often an abnormal GFR at follow-up than patients treated with one only. Although the number treated with more than one NSAID was small the difference was statistically significant. Treatment of the nephritis with corticosteroids was associated with a more serious outcome, but those who were treated with steroids had also a more serious disease at admission.

Discussion

The peculiar syndrome of acute or subacute tubulointerstitial nephritis associated with the nephrotic syndrome seen after NSAID treatment has given rise to much speculation about the underlying mechanisms. In a previous review [7] NSAID nephropathy was considered as a clinical entity distinct from drug-associated acute tubular interstitial nephritis (ATIN), not only because of the frequent occurrence of heavy proteinuria, but also because in contrast to ATIN it was preferentially seen in old age, and the onset occurred after much longer exposure to the drug and was followed by signs and symptoms of systemic hypersensitivity in a few cases only. It could also be added that the course in NSAID nephropathy most often is milder and more protracted.

Since then many more cases have been reported allowing a more detailed description of the syndrome. First, systemic hypersensitivity seems to be more frequent than reported previously. Many case reports were incomplete on that point, probably because the relevant analyses were not performed. After exclusion of the cases with insufficient information it appeared that features of hypersensitivity were just as frequent in AN as has been reported in drug-induced ATIN, and about 50% of the rest presented with evidence of hypersensitivity also.

The high frequency of allergic features indicates that drug hypersensitivity may also trigger NSAID nephropathy. Also suggestive is analyses of the mononuclear, interstitial cells. In one study they were entirely T-cells [26]; in another study, 80% were T-cells and of the 20% B-lymphocytes the great majority were IgE-bearing [62] and treatment after discontinuation of the drug with another NSAID did not result in relapse [64, 69].

The lower frequency of allergic symptoms in patients with heavy proteinuria could be explained by a time-factor. As these patients had a milder and more protracted course they may have sought medical help at a time where the allergic reactions had disappeared.

The higher mean age in NSAID nephropathy compared with ATIN does not necessarily mean different mechanisms, but rather that the indication for NSAID treatment most often is a disease of middle and old age,

whereas antibiotics, the commonest cause of drug-associated ATIN, are used in patients of all ages.

Heavy proteinuria with the nephrotic syndrome is not unique for NSAID nephropathy either, but is also known from drug-induced ATIN [74–76]. Linton *et al.* [77] found 0.4 to to 1.7 g urine protein 24 h^{-1} in nine cases; Pusey *et al.* [78] noted close to nephrotic range proteinuria in three of seven cases; and Galpin *et al.* [79] found similar and even higher degrees of proteinuria in three of 14 cases.

Also suggestive of common mechanisms is that fusion of the epithelial foot processes, a constant finding in patients with heavy proteinuria, is common in patients with drug-induced ATIN also, as well as in NSAID-induced AN. In the study by Pusey *et al.* [78] for instance, a consistent finding on EM was partial foot process fusion; and in the present study this was seen also in five of the eight patients with AN, whose biopsy was studied by EM.

Thus, it is not self-evident that drug-associated ATIN and NSAID nephropathy are different entities with different mechanisms; both diseases may be effects of immunologic reactions against the offending drug. But why had some patients heavy proteinuria?

A toxic effect on the podocyte is unlikely because in other patients, NSAID treatment is not followed by proteinuria; on the contrary, NSAIDs have been used to ameliorate proteinuria in the nephrotic syndrome [80]. Neither could immune complex formation be responsible, at least not in patients with MC and focal sclerosis. Such formation may participate in MGN, but proteinuria was not associated with amount of glomerular deposits, and patients with MGN had less proteinuria and also a milder course than patients with MC. Hence, a humoral mechanism of proteinuria seems likely, as suggested by others also [26]. Cells of the immune system are said to produce one or more intrinsic, humoral factors, probably lymphokines, which change the permeability of the podocyte [81], a mechanism considered likely in childhood MC [82].

That an allergic reaction is responsible is supported by the absence of major clinical, laboratory or pathologic differences between drug-induced ATIN and NSAID-induced AN. The differences between drug-induced ATIN and NSAID nephropathy with heavy proteinuria may be quantitative rather than qualitative. In drug-associated ATIN and in NSAID-associated AN the immune system reacts abruptly; the patient seeks medical advice at an early stage of the disease where most features of hypersensitivity are still present. Treatment with the offending drug is therefore discontinued early in the course before a more substantial production of lymphokines has started. In patients with heavy proteinuria the symptoms appeared after months or years. The torpid course may allow the acute allergic symptoms to abate and give more time for the lymphokines to induce podocyte disturbances and thus pronounced proteinuria.

A crucial question remains: if NSAID nephropathy is due to hypersensitivity, why are the reactions much slower and milder after NSAIDs than after other drugs? The answer may be that the offending NSAID holds back the reactions it has started itself. NSAIDs are thought to exert their effect by suppressing a variety of inflammatory mediators, many of which participate in anaphylactic and cell-mediated hypersensitivity [83, 84]. As a consequence, the very reactions that are responsible for the tissue damage in NSAID nephropathy may be weakened or delayed by the same drug that started the reactions.

Most likely, the formation of immune complexes in NSAID nephropathy is secondary to the increased permeability to macromolecules and does not necessarily contribute to the renal damage. More complexes may be formed the longer time the increased permeability persists and more easily in patients with a hyperreactive or dysregulatory immune system. That proteinuria was associated with treatment time, but not with amount of glomerular deposits, although the two latter were associated with each other, also indicates that lymphokine production is more important for the creation of proteinuria than the formation of immune complexes. In accordance, a large number of clinical and experimental observations have shown that even pronounced MGN may appear without inducing proteinuria or renal failure [85].

Most important in the management of NSAID nephropathy is to discontinue treatment with the offending drug. A worsening of renal function was seen in all patients who continued NSAID treatment, and with few exceptions all patients improved after discontinuation of the drug, in most cases with total remission.

Conclusions

The nephritides seen after treatment with NSAID are not necessarily separate entities distinctly demarcated from each other and with separate mechanisms, but rather a continuous spectrum of renal responses to a state of hypersensitivity against the drug. The clinical, laboratory and pathologic variations are most likely determined by the type and strength of the immunologic response and the length and magnitude of the drug exposure. The milder and more protracted course in NSAID-induced nephropathy compared with drug-induced ATIN may be due to a delay of the immunologic reactions induced by the offending NSAID itself causing the immune system to work ineffectively and in slow-motion.

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Tables with more comprehensive information can be acquired from the author.

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