Hardly a harmless analgesic

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Introduction

Membranous nephropathy (MN), the most common cause of nephrotic syndrome in adults, is usually idiopathic, with an identifiable cause in only about 20% of cases.[1] Causes of secondary MN include various auto-immune diseases, neoplasms, infections, and drugs such as gold or penicillamine. Although minimal-change glomerulopathy associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDS) is a well established clinical entity,[2,3] the association between NSAID use and MN is less well known.

A review of the literature revealed 14 separate cases of MN associated with NSAID use.[4-7] In each case, other known causes of MN were excluded, and prompt resolution of the nephrotic syndrome was noted after cessation of NSAID therapy. The reported NSAIDs include diclofenac, ibuprofen, ketoprofen, phenylbutazone and sulindac.

We report here our experience with a case of MN and discuss the possible pharmacological/toxicological mechanisms of how NSAIDs might cause this pathology.

Case Reports

A 68 year old woman with long standing hypertension was hospitalised (Parirenyatwa Hospital, Harare, Zimbabwe) one week after the sudden development of oedema refractory to frusemide. Two months before admission she had a flu-like illness with myalgias, fever, fatigue, cough, and sore throat. All symptoms except the fatigue resolved after a seven day course of penicillin. She had a long history of pain from osteoarthritis for which she had been taking 75 mg of diclofenac twice daily for two to three years.

Physical examination revealed a blood pressure of 115/70 mm Hg, scattered bibasilar crackles, and 2+ pitting oedema to the knees with trace oedema in the thighs. Her full blood count was normal with the exception of 9% eosinophils (normal, <4%). Her total leukocyte count was 8.4 x10^9 /L, with total eosinophils 0.756 x10^9/L. Her serum creatinine concentration was 80 mmol/L, with a urea of 7.5 mmol/L. Her serum

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albumin was 12 g/L, and her cholesterol was 13.9 mmol/L. Urinalysis revealed 4+ protein with 11 to 20 leukocytes per high power field and occasional granular casts. Urine gram stain for eosinophils yielded negative results. A 24 hour urine collection revealed a creatinine clearance of 1.34 mL/s (80 mL/min) and a total protein excretion of 10.8 g/d.

Diclofenac was discontinued and diuresis was initiated with a regimen of bed rest and frusemide. In addition, enalapril was started at 2.5 mg/d, and a percutaneous renal biopsy was performed. The pathological findings included normocellular glomeruli with scattered fuchsinophilic subepithelial deposits on trichrome stain and patchy tubular atrophy with a few small foci of lymphocytic interstitial infiltrates without eosinophils. Immunofluorescence revealed diffuse granular capillary wall staining for both IgG and C3, 2+; kappa and lambda light chains, 1+; and segmental granular staining for IgA, 1+. Electron microscopy revealed scattered small electron-dense subepithelial deposits with rudimentary spike formation, and a diagnosis of stage 1 MN was made (Figure I).

Figure I: Subepithelial electron dense deposits (arrows) with minimal glomerular basement membrane spike formation (original magnification x 17 500).

With conservative therapy, the patient had resolution of her oedema within eight weeks of stopping use of diclofenac and a decline in 24 hour protein excretion to 1.2 g at seven weeks and to only 0.05 g at 22 weeks. She remained well 12 months later, with no evidence of recurrence.

Discussion

Since cessation of NSAID use may be curative in these patients, it is essential for practitioners to be aware of this association and to elicit a careful medication history in all patients who present with proteinuria. Given the ubiquitous use of NSAIDs and the fact that MN is a common cause of nephrotic syndrome in adults, this problem is almost certainly under recognised.

Published series report at least 10% of early stage MN is associated with NSAID use.[4-7] For several reasons, however, this most likely represents a minimum number. First, obtaining a history of NSAID use may be difficult, because many patients do not think of over-the-counter drugs as "medicines." Second, some nephrotic patients known to be using NSAIDs do not undergo renal biopsy because of presumed minimal-change disease. Finally, the retrospective nature of most studies (as in our case) limits the information available to that in the medical record.

Clinical features that may help to distinguish NSAID associated from idiopathic MN are the relatively rapid onset of symptoms, the rapid remission after NSAID withdrawal, and the absence of recurrent disease. Although the pathological features of NSAID-associated MN are indistinguishable from those seen in idiopathic MN, many of the reported cases of NSAID associated MN are stage 1, perhaps reflecting early patient presentation as a result of the rapidity of symptom onset.

Nephrotic syndrome related to the use of NSAIDs has usually been associated with minimal-change glomerulopathy. NSAID associated minimal-change disease has many clinical features in common with NSAID associated MN, including a variable period of NSAID use before symptom onset, rapid symptom onset, rapid improvement after NSAID withdrawal, and absence of systemic allergic symptoms such as fever, rash, and eosinophils.

Causative mechanisms responsible for development of analgesic nephropathy.

Pathogenesis of NSAI induced nephropathy most likely involves several physiological and biochemical events:

1. Counter-current concentration in the kidney may be responsible for the site-specific accumulation of NSAID in the renal medulla, leading to several-fold higher concentration of these drugs than in the plasma.
2. NSAID by inhibiting renal cyclooxygenase can cause an imbalance in the production of renal vasoconstrictor prostaglandins thus causing renal vasoconstriction and medullary ischaemia.
3. NSAIDs may undergo bioactivation[3] by medullary prostaglandin synthetase, leading to the formation of highly reactive metabolites (free radicals). Although it remains unclear whether a causal relationship exists between high concentrations of free radicals and concurrent nephropathy, it seems unlikely that the two are simply confounding variables or epiphenoma that are unrelated.
4. Cell damage and cell death (necrosis) in the renal papilla may occur due to the disruption of cell function by the covalent binding of reactive metabolites to DNA and other essential macromolecules.

Good prospective data on the long term risk of chronic NSAID therapy and further research on the molecular mechanisms of toxicity is clearly needed to establish the role of NSAIDs in this iatrogenic condition. Continually increasing sales and wider availability (over-the-counter) of NSAIDs may lead to increased prevalence of this clinical syndrome. Diligent history taking of drug use, signs of potential dependence or abuse of combination analgesics may alert physicians to the possibility of analgesic nephropathy, that can lead to discontinuation of the offending drug and prevention of potentially fatal chronic renal failure.

Conclusion.

Despite the fact that conclusions regarding causation cannot be derived from a retrospective case such as ours, the rapid resolution of symptoms after NSAID withdrawal is highly suggestive of a causal role for diclofenac on the MN. Use of NSAIDs should, therefore, be considered in the differential diagnosis of membranous glomerulopathy. Because the prognosis for these patients is good after withdrawal of the offending NSAID, a history of NSAID use should be diligently sought in any patient who presents with MN. In our case there is a remote possibility that the angiotensin converting enzyme inhibitor (enalapril) may have contributed to the resolution of the proteinuria as this is well described in the literature. However, given the rapidity of the recovery from the severe proteinuria (less than six months) we felt that the improvement was largely attributable to the withdrawal of diclofenac.

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