Case Report

Acute renal failure induced by nimesulide in a patient suffering from temporal arteritis

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Key words: interstitial nephritis; nimesulide; NSAIDs; renal adverse effects; temporal arteritis

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) include a vast number of compounds, which steadily increases. They are prescribed in a large number of patients for a diverse group of diseases and as a consequence, the incidence of side-effects is increasing too [1]. Renal adverse effects of these drugs are mainly due to inhibition of prostaglandin synthesis and include acute reversible 'vasomotor' renal failure and disorders of water, sodium and potassium balance. Acute interstitial nephritis, nephrotic syndrome and chronic renal injury, are less common side-effects [2].

Nimesulide, a new generation NSAID of the sulphonanilide class has potent anti-inflammatory, analgesic and antipyretic activities. It is claimed that it causes less adverse effects [3–5]. To our knowledge, clinical reports concerning the induction of acute renal failure after the administration of nimesulide, are not available [5]. We describe a case of a patient with acute oliguric renal failure following the administration of this drug.

Case report

A 68-year-old, non-diabetic woman with known diffuse arteriosclerosis and coronary heart disease, was hospitalized, on 1st July 1995, in an internal medicine department because of low grade fever of sustained pattern and generalized myalgias. An extensive investigation of the patient was done which, apart from the findings of severe arteriosclerosis of the large vessels, did not reveal any other disease. Renal function was normal, assessed by serum urea and creatinine levels and negative findings of the urinary sediment. She returned home, on 12th July 1995, and awaited the result of the biopsy of the temporal artery and took the advise to treat muscle pains with nimesulide at 100 mg once a day. No other drug was prescribed or was taken by the patient, except nifedipine 20 mg bid, for her coronary heart disease. Having received only one tablet of the drug, after 1 day of leaving the hospital she was admitted to the same department, where acute oliguric renal failure was discovered, which was accompanied by hyperkalaemia and proteinuria. Table 1 summarizes the main laboratory findings of the patient, before and after treatment with nimesulide. Because of the steady deterioration of renal function, on 15th July she was referred to the nephrology department. On admission, the patient was normotensive, and had no clinical signs and symptoms of congestive heart failure or volume depletion and neither fever or rash were present. She had proteinuria, impaired renal function and anaemia (Table 1). The report of the biopsy of the temporal artery revealed findings of classic temporal arteritis (Fig. 1) while the renal biopsy that followed, 8 days after her admission in the nephrology department, showed ischaemic lesions of a great number of glomeruli (10/14) and tubules, accompanied by minimal endocapillary lesions in the preserved glomeruli. A diffuse infiltration of lymphocytes and plasma-cells was found in the interstitium, indicating active lesions of interstitial nephritis, similar to those described in NSAID nephritis (Fig. 2). A search for cholesterol emboli was negative in the given tissue sample. The immunofluorescence study showed sparse granular deposition of humps like C3 and IgM positive, on capillary walls. Corticosteroid treatment was begun (methylprednisolone 32 mg/day) and the patient showed a progressive improvement of her renal function. She left the hospital in good condition, with normokalaemia, negative urine sediment and low values of serum urea and creatinine levels (Table 1). On December 15th 1995, she had normal serum values of urea and creatinine.
Table 1. Patient's characteristics before and after the use of nimesulide as well as at her discharge

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ht (%)</td>
<td>32</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>Leukocytes/cm²</td>
<td>8750</td>
<td>7500</td>
<td>6800</td>
</tr>
<tr>
<td>(N, L, M, E%)</td>
<td>65,25,8,2</td>
<td>62,28,8,2</td>
<td>66,28,5,1</td>
</tr>
<tr>
<td>Sedimentation rate (mm/h)</td>
<td>132</td>
<td>125</td>
<td>42</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>42</td>
<td>109–250</td>
<td>61</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1</td>
<td>3.3–10</td>
<td>1.7</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>144</td>
<td>137</td>
<td>140</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>4,1</td>
<td>6</td>
<td>4.6</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>4,1</td>
<td>6,9</td>
<td>6</td>
</tr>
<tr>
<td>Proteinuria (g per 24 h)</td>
<td>No</td>
<td>1,5</td>
<td>No</td>
</tr>
</tbody>
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N = neutrophils, L = lymphocytes, M = monocytes, E = eosinophils.

Fig. 1. Temporal artery biopsy: Monocytic infiltration of the media and adventitia (haematoxylin and eosin stain). Insert: disruption of the elastic lamina (Elastic-van Gieson stain, × 40).

Discussion

NSAIDs may cause fluid and electrolyte disorders and both acute and chronic renal failure. Haemodynamically mediated acute renal failure is the most common form of acute renal failure associated with the use of these drugs and is dose-related. It develops almost exclusively in predisposed patients, like those with impairment of renal, cardiac and hepatic function as well as in elderly individuals, where an increased action of vasodilating prostaglandins is required to maintain a sufficient renal perfusion. It is not associated with structural damage and is usually reversible [2,6–8].

Acute interstitial nephritis due to NSAIDs, is rare and is not dose-related. Usually the development of this lesion occurs after days, weeks, months and even years of NSAIDs administration and most of the time, it is associated by heavy proteinuria. These features differ from those seen in interstitial nephritis caused by other drugs, in which the onset of nephritis is earlier and with evidence of an allergic reaction (rash, fever, eosinophiluria and eosinophilic infiltrate of interstitium) and usually without nephrotic proteinuria. Diagnosis of NSAIDs nephropathy is made by renal biopsy, which shows slight glomerular abnormalities with negative immunohistology (minimal change disease) and tubulointerstitial oedema with infiltrate that consists predominantly of T-lymphocytes and to a lesser extent of other cells [9,10].

The patient that we describe has some peculiar features that need discussion. She was suffering from
Fig. 2. Renal biopsy showing glomerular and tubular ischaemia (left) and heavy predominantly monocytic interstitial infiltration (right) (PAS stain × 40).

Fig. 3. Most of the inflammatory cells show positive cytoplasmatic stain for CD8 lymphocyte marker (ABC method, Moab DACO CD8, DK25, × 100).
temporal arteritis and although this disease is recognized as a systemic vasculitis, renal involvement is very uncommon. In rare cases, widespread vasculitis involving renal arteries or microscopic polyarteritis can be seen [11,12]. However, this is not the case with our patient, in whom the renal tissue sample showed no evidence of vasculitis or active glomerulonephritis. Our patient was also suffering from severe atherosclerosis and this process is often associated with cholesterol emboli and renal failure, which is usually irreversible. However, the clinical course and the negative findings for cholesterol emboli in the tissue sample were not suggestive for this entity.

The acute onset of oliguric renal failure and hyperkalaemia, after the administration of the drug, was compatible with inhibition of prostaglandin synthesis in an elderly patient with histological findings of ischaemic glomeruli, i.e. with a haemodynamic effect of the drug in a predisposed patient. On the other hand, among these sclerotic glomeruli, a diffuse interstitial infiltrate of activated lymphocytes was noted. The ratio of CD4/CD8 T-cells, which is in favour of CD8 T-cells, represents an interesting finding that enhances the hypothesis of an acute NSAIDs nephritis taking place in the tissue sample (Fig. 3). The predominance of T-lymphocytes in the interstitial infiltrate is a common finding in this type of nephritis and in many studies, a ratio of CD4/CD8 T-cells in favour of CD8, was found. In the opinion of the authors this finding, as in the present case, is an argument in favour of an immune mediated interstitial nephritis, but the exact immune pathogenesis has not been clarified. One can speculate a role of these activated T-cells on the release of lymphokines that can possibly cause increased glomerular permeability and proteinuria, which is common in this process [9,12]. The observation that different NSAIDs may cause the same lesions, has led to the hypothesis that this injury is a consequence of inhibition of renal cyclo-oxygenase. This can lead to the stimulation of one other pathway of arachidonic acid metabolism, that of lipo-oxygenase, with the release of leukotrienes, which are potent chemotactic factors for lymphocytes [10,13].

Another histological observation in patient’s renal biopsy was that fibroblasts were not present in the active infiltrate of cells found, indicating that an acute inflammatory process was indeed going on in the interstitium.

We can conclude, that in this patient, with mainly age and atherosclerosis related ischaemic glomeruli, where vasodilating prostaglandins were maintaining an apparent normal renal function, nimesulide has provoked acute oliguric renal failure and hyperkalaemia. Such renal effects have not been documented in animal models, unless extremely high doses of nimesulide were administered. In humans they might be provoked, however, in clinical settings where effective plasma volume is reduced, as in the present case [14]. In addition, at 8 days after receiving nimesulide, renal biopsy revealed an active infiltrate of cells which corresponded to acute interstitial nephritis. These observations indicate that this new drug can provoke, at least in predisposed elderly patients, acute renal failure as a result of acute tubulo-interstitial nephritis, although remote, haemodynamic effects cannot be completely excluded as a contributory factor.

Acknowledgements. The authors wish to acknowledge Dr A. Galinas for his kind support in completing this work.

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Accepted in revised form: 19.2.97

Received for publication: 6.12.96