PART XXXVII

## NEPHROTOXICITY—AMINOGLYCOSIDES

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# MEFENAMIC ACID NEPHROPATHY – A SPECTRUM OF RENAL LESIONS

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## Summary

Pre-renal uraemia, papillary necrosis, and systemic hypersensitivity with vasculitis have been reported as causes of renal failure due to mefenamic acid. We report seven further cases of renal failure due to the drug, including two with interstitial nephritis on biopsy. Thus mefenamic acid may result in renal damage by a variety of mechanisms.

## Introduction

Several cases of structural renal damage and functional renal impairment caused by mefenamic acid have been reported in the literature [1–7]. We report seven further cases of renal failure related to mefenamic acid; in two patients renal biopsy showed an acute interstitial nephritis, but different mechanisms may have been implicated in the other patients.

## Patients

The seven patients, four male and three female, were seen within two years. Four patients (cases 1, 5–7) presented as acute uraemic emergencies, while the other three patients were found co-incidentally to have renal impairment whilst being investigated for diarrhoea and/or vomiting. All but one patient (case 4) had been taking mefenamic acid for four weeks or less prior to renal failure being detected. Three patients (cases 1, 4 and 6) had been taking thiazide diuretics for at least 12 months before investigations, and all three continue to take thiazides without apparent ill effects.

All patients had developed at least one, and usually two, of the classical side effects of mefenamic acid – skin rash, vomiting, diarrhoea – before renal failure was diagnosed.

The clinical features, drug history, and renal function of these patients are shown in Tables I and II. All patients showed a substantial improvement in

renal function on withdrawal of mefenamic acid, but no patient recovered normal renal function as judged by plasma creatinine concentration.

TABLE I. Patient details and drug history in seven cases of mefenamic acid nephropathy

| Case Number | Age | Sex | Underlying disease requiring analgesia | Daily dose of mefenamic acid (g) | Duration of therapy (weeks) | Concomitant therapy |
|---|---|---|---|---|---|---|
| 1 | 57 | M | Acute low back pain | 1.5 | ½ | Oxprenolol Xipamide |
| 2 | 74 | M | Rheumatoid Arthritis | 1.5 | 4 | Nil |
| 3 | 60 | M | Post-op analgesia | 1.5 | ½ | Prochlorperazine |
| 4 | 65 | M | Osteo-arthritis | 1.5 | 20 | Cyclopenthiazide |
| 5 | 80 | F | Painful knee | 0.75 | 2 | Nil |
| 6 | 89 | F | Acute | 1.5 | 3 | Cimetidine, Quinine, Paracetamol, Metoclopramide, Bendrofluazide |
| 7 | 64 | F | Soft tissue injury | 1.5 | 3 | Nil |

*Renal histology*

Two patients (cases 2, 4) underwent renal biopsy. Both displayed similar histological features with a florid acute interstitial nephritis.

The biopsy from case 2 showed global sclerosis in six of 10 glomeruli. The remaining glomeruli showed mild mesangial expansion and patchy basement membrane reduplication. Arterioles showed hyalinosis and intimal proliferation. The interstitium was expanded and fibrotic with a brisk mononuclear cell infiltrate.

Only two of 20 glomeruli in case 4 were sclerosed. Glomerular changes were similar to case 2 while the arteriolar and interstial morphology was identical (Figure 1).

Ultrastructural examination by electron microscopy revealed the same features in both biopsies, viz: mesangial expansion, endothelial cell hypertrophy, loss of fenestration, endothelial vacuolation and extension of endothelial cell processess into the basement membrane. Some capillary loops contained cell fragments with the characteristics of atypical large platelets. Arterioles showed localized atrophy of the media, massive eccentric accumulation of subendothelial material and irregularity of the endothelium itself (Figure 2).

TABLE II. Clinical features, renal function and outcome in seven cases of mefenamic acid nephropathy

| Case No | Clinical features | | | | | Plasma creatinine (μmol/L) | |
|---|---|---|---|---|---|---|---|
| | Rash | Vomiting | Diarrhoea | Oliguria | Other | On admission | Latest |
| 1 | + | + | + | + | Severe systemic illness; respiratory failure, cardiac arrhythmias, haemodialysis | 720 | 140 |
| 2 | | + | + | | Biopsy: interstitial nephritis | 550 | 330 |
| 3 | | + | + | | Dehydrated | 300 | 150 |
| 4 | | | + | | Barium enema, sigmoidoscopy normal. Biopsy: interstitial nephritis | 250 | 160 |
| 5 | + | + | + | + | Mild dehydration. Steroids prescribed for 7 days | 1400 | 260 |
| 6 | | + | | | Uraemic features, only mildly dehydrated | 850 | 175 |
| 7 | | + | + | + | Acute uraemic emergency, spontaneous recovery | 1350 | 300 |

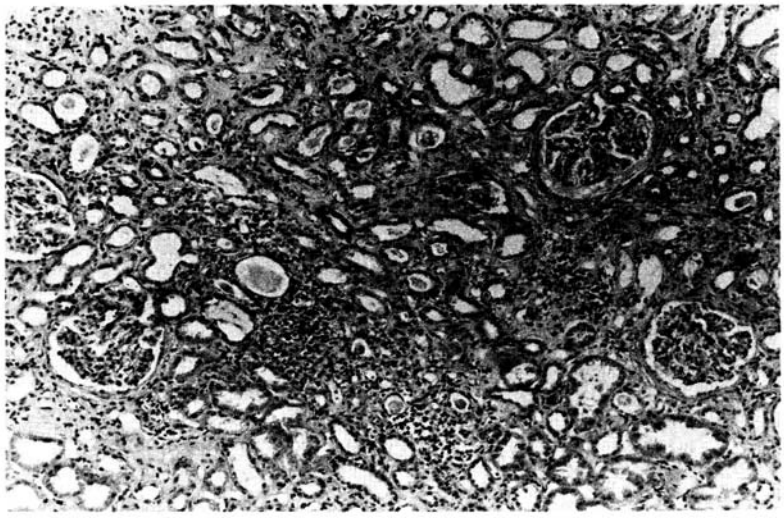

Figure 1. Case 4. Marked interstitial fibrosis with a heavy mononuclear cell infiltrate. The glomeruli display mild mesangial hypercellularity. Some peripheral loops are thickened. (Haematoxylin and eosin, x 16 – reduced for publication)

Figure 2. Case 2. Endothelial cells show irregular vacuoles containing cellular material. Cellular interpositioning in the capillary wall is present and some of these cell processes are continuous with the endothelial cells. Subendothelial material and epithelial foot process fusion are present (Lead and uranium x 7,500 – reduced for publication)

## Discussion

All these patients were found to have moderate to very severe renal impairment whilst taking mefenamic acid, and all showed improvement on withdrawal of the drug. The two patients whose kidneys were biopsied had a florid acute interstitial nephritis, and in the absence of any other agent likely to have caused this reaction, it seems reasonable to ascribe it to mefenamic acid. Case 1 presumably had a systemic hypersensitivity reaction as a cause of his renal failure, but was not biopsied. Several of the other patients were salt and water depleted on admission (due to diarrhoea and/or vomiting), but the severity of renal failure with a proportionate rise in both creatinine and urea in these cases was highly atypical for pre-renal uraemia alone. The prompt and striking improvement in renal function in all cases on withdrawal of mefenamic acid points to this drug as the responsible nephrotoxic agent. No patient regained normal renal function, but this is not entirely unexpected in view of the marked interstitial fibrosis found on renal biopsy.

It is generally recognized that all non-steroidal anti-inflammatory drugs are nephrotoxic. The postulate that inhibition of prostaglandin synthesis by medullary interstitial cells causes medullary ischaemia is still tenable. Non-steroidal anti-inflammatory drugs are thought to inhibit the synthesis of prostaglandin E [8] which has vasodilator properties. The effects on prostaglandin synthesis may be reflected in the atypical and large platelets identified in our patients. The endothelial abnormalities suggest an effect on these cells by mefenamic acid but whether or not this is mediated or related to prostaglandin activity is not clear. The interposition of mesangial cells may also be related to the drug, but some of the glomerular changes must be attributed to existing arterial disease and age. Of note is the precipitate deterioration of renal function in patients with systemic lupus which follows the administration of non-steroidal anti-inflammatory drugs [9]. It has been postulated that prostaglandins may be relevent when the renal circulation has been compromised [10] and it is interesting that both patients biopsied had arteriolar hyalinosis. Thus it is likely that pre-existing mild renal impairment predisposed our patients to acute drug-related renal injury.

Although there are several reports in the literature of renal impairment related to mefenamic acid, there are few reports of interstitial nephritis due to the drug [2, 5–7]. The Committee of Safety of Medicines (CSM) however, is aware of five further unreported cases of interstitial nephritis related to mefenamic acid. (CSM – personal communication.)

Malik et al [3] reported a florid systemic fatal illness related to mefenamic acid, apparently similar to case 1 in our series. On the other hand, Robertson et al [1] reported one of their patients with papillary necrosis due to mefenamic acid, and one with aggravation of previously documented renal impairment.

Thus mefenamic acid nephropathy is an imprecise term, and encompasses interstitial nephritis, systemic hypersensitivity, papillary necrosis and aggravation of previous renal disease by salt and water depletion.

In total, the manufacturers of the drug and the CSM are aware of 16 cases in the United Kingdom of nephrotoxicity due to mefenamic acid (in addition to the 7 cases reported here), but in several of these cases the relationship between taking the drug and the discovery of renal failure is not very close (CSM – personal communication; Warner-Lambert (UK) Ltd – personal communication).

In the 10 year period 1972–1982, eight million prescriptions for mefenamic acid were prescribed (Warner-Lambert (UK) Ltd – personal communication). Thus the total of 23 cases of mefenamic acid nephropathy do not seem to constitute a major drug hazard. Nonetheless, in the seven cases reported here, and also in all the other cases for which sufficient data is available, renal failure had been preceded by a rash, vomiting or diarrhoea. Clearly if any of these typical side effects develop in a patient taking mefenamic acid, the drug must be immediately stopped in order to avoid potentially severe and only partially reversible renal damage.

## References


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