Sir,

Drug-induced acute interstitial nephritis (AIN) can cause end stage renal failure. Withdrawal of imputable drugs is the best treatment, and requires early recognition. We report the first two biopsy-proven cases of fluindione-related AIN indicating that fluindione must be included in the list of imputable drugs.

**Case 1.** A 72-year-old man was admitted to our unit for acute renal failure (serum creatinine 353 μmol/l vs 107 μmol/l at baseline). He had started fluindione for atrial fibrillation five weeks before. Clinical examination was normal. There was no eosinophilia. Urine protein/creatinine ratio was 25 mg/mmol, containing low molecular weight protein without albumin. There was no haematuria or pyuria. Renal ultrasonography was normal. Fluindione was stopped at admission. Transjugal renal biopsy disclosed interstitial lymphocytic infiltration with severe tubulitis. Immunofluorescent studies revealed no immune deposits. The renal function returned to baseline level 2 weeks after fluindione was stopped, without corticosteroid therapy.

**Case 2.** An 80-year-old woman, who had experienced a phlebitis treated with fluindione 4 months earlier, was admitted to the medical unit for contralateral ilio-femoral phlebitis. Her baseline serum creatinine level was 100 μmol/l due to nephrosclerosis. After initial heparin treatment, fluindione was reintroduced. Twelve days later, serum creatinine level was 181 μmol/l, and then rose to 374 μmol/l. She was transferred to our renal unit, and her clinical examination was normal. There was no eosinophilia. Proteinuria was 0.5 g/day without albuminuria or immunoglobulin light chain: there was no haematuria or pyuria. At ultrasound exploration, kidneys appeared normal, and vena cava and renal veins were free of thrombus. Fluindione was stopped and substituted by heparin. Renal biopsy revealed a marked diffuse interstitial infiltration with mostly lymphocytes and a few polymonocytes and cells and mild tubulitis. Immunofluorescent studies were negative. Soon after, the patient died of pulmonary embolism despite intensive medical care.

In these two cases, fluindione was implicated as the likely causative agent. In Case 1, the renal function improved after fluindione was withdrawn without corticosteroid treatment. No follow-up was possible in Case 2. As no other new drug was introduced, we consider these cases as fluindione-induced immuno-allergic AIN. Only two cases have previously been reported [1,2], but none was biopsy-proven. In contrast with our report, these cases presented extra-renal involvement including hyperthermia associated with cutaneous manifestations. Delays between fluindione introduction and disease onset were 3 and 8 weeks, which is comparable with the 5-weeks delay observed in Case 1, but longer than the usual 10 days delay in drug-induced AIN [3]. In Case 2, the delay was 12 days, but as the patient had already been exposed to fluindione, it is compatible with a re-exposure immuno-allergic side-effect.

Physicians should be aware of this severe side-effect and of its potential clinical latency.

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**Fluoroquinolone-induced acute interstitial nephritis in immunocompromised patients: two case reports**

Sir,

Nephrotoxic side effects related to the use of fluoroquinolones (FQ) are relatively rare, and only four cases were reported with the newer fluoroquinolones (levofloxacin and norfloxacin) [1]. The risk factors and mechanisms were largely unknown. We described two biopsy-proven cases of levofloxacin and ciprofloxacin induced acute interstitial nephritis (AIN) in immunocompromised patients.

**Case 1.** A 41-year-old Chinese female with known history of systemic lupus erythematosus was treated with levofloxacin 200 mg twice a day for 10 days because of urinary tract infection. At the first presentation, biochemical tests were normal except lymphopenia (lymphocyte count, 1067/μl) and bacteriuria. However, fever developed after 1 week of levofloxacin treatment. Physical examination revealed excessive extracellular fluid volume. Laboratory studies showed serum creatinine 5.4 mg/dl, serum urea nitrogen (BUN) 27 mg/dl, WBC count 8610/μl with 60.4% neutrophils, 22.9% lymphocytes and 2.4% eosinophils. Urinalysis revealed WBC 25–50 per high-power field (hpf) and bacteriuria. A diagnosis of AIN was made.
Serum creatinine decreased to 1.08 mg/dl 10 days after admission. She was discharged uneventfully.

Case 2. A 74-year-old Chinese male was admitted to our hospital because of high fever. At that time, serum creatinine was 1.4 mg/dl and WBC count was 1350/dl with 8% neutrophils and 62% lymphocytes. Intravenous cefepime 2 g per 12 h were used for neutropenic fever. Blood culture revealed *Pseudomonas aeruginosa* bacteraemia. After fever subsided, antibiotics were shifted to oral ciprofloxacin 500 mg twice a day on day 7. However, nausea and vomiting developed 4 days after ciprofloxacin treatment. Physical examination revealed tachypnea. Laboratory studies were serum creatinine 6.4 mg/dl, BUN 57 mg/dl, WBC count 8220/μl with 75.2% neutrophils, 19.3% lymphocytes and no eosinophils. Urinalysis revealed WBC 5–10/hpf and RBC 10–25/hpf with WBC casts. Because of oliguria and uraemic symptoms, haemodialysis was performed on day 16 when peak serum creatinine was 11.4 mg/dl. Renal biopsy demonstrated normal glomeruli, interstitial infiltration with mononuclear cells, negative immunofluorescent expression, and no electron dense deposits. A diagnosis of AIN was established. Three haemodialyses were conducted. Serum creatinine decreased to 1.4 mg/dl on day 37. He was discharged uneventfully.

Comment. The incidence of elevated serum creatinine levels related to FQ range from 0.2 to 1.3% [2]. However, levofloxacin-induced AIN is relatively rare. One case of biopsy-proven granulomatous interstitial nephritis and another case of clinically suspected AIN with purpura had been reported [3,4].

Neutropenia and lymphopenia as presented in our two cases might be risk factors of FQ-induced nephrotoxicity. Cancer patients, combined nephrotoxic agents, ciprofloxacin and old age (>50 years) were observed more commonly in the reported cases of FQ-induced nephrotoxicity as proposed by Lomaestro [1]. Several reported cases showed that cancer patients especially during neutropenic fever period after chemotherapy might undergo FQ-induced AIN [5]. On the other hand, lymphopenia was also observed in FQ-induced AIN in one reported case and our first case [3]. Cell mediated hypersensitivity was supposed in FQ-induced AIN [1]. Ciprofloxacin could modulate immune system and induce the expression of interleukin-2 and interferon-gamma in human T-lymphocytes [6]. We propose that sensitized lymphocytes expanding quickly by FQ-induced cytokine reaction during the recovery of leukopenia result in FQ-induced AIN.

In summary, both older and newer fluoroquinolones, ciprofloxacin and levofloxacin, could cause acute interstitial nephritis or oliguric acute renal failure that requires haemodialysis. Clinicians should be aware of these adverse effects especially in neutropenic and lymphopenic patients.

Conflict of interest statement. None declared.

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