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Flucloxacillin induced acute renal failure

Background
Acute interstitial nephritis is a less frequently reported adverse effect of flucloxacillin compared with other well known associations such as hepatotoxicity.

Objective
This article describes the conservative management of a case of flucloxacillin induced acute renal failure, and reviews the available evidence on the treatment of drug induced acute interstitial nephritis, including the use of corticosteroids.

Discussion
Drug induced acute interstitial nephritis can be managed conservatively by cessation of the suspected offending drug in many cases. Referral should be made to a nephrologist, with consideration given to renal biopsy, followed by trial of corticosteroids, if renal function does not improve within 7 days of drug cessation.

Case study

Mr A, 87 years of age, presented with a warm, red, swollen collection anterior to his left knee. This was clinically diagnosed as pre-patellar bursitis. An aspirate of the bursa before commencement of antibiotics yielded 2 mL of serous fluid. Culture of the aspirate did not grow any organisms. Ultrasound confirmed pre-patellar bursitis, without evidence of joint effusion. Blood and urine cultures were negative. His urea, electrolytes and creatinine (UEC) were normal: serum creatinine 80 µmol/L, urea 6.0 mmol/L, with an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m^2.

On day 3, the redness around Mr A's left knee spread. He was started on intravenous flucloxacillin 1 g four times per day for empirical treatment of presumed cellulitis. On day 9, Mr A's UEC revealed:

- serum creatinine 210 µmol/L (normal range: 60–120 µmol/L)
- urea 16.5 mmol/L (normal range: 2.9–8.2 mmol/L).

His creatinine continued to rise, reaching a peak of 258 µmol/L, with a urea of 17.4 mmol/L on day 14. Mr A had no previous history of renal impairment or diabetes. There had been no change in his medications, except for the introduction of flucloxacillin on day 3. Therefore, flucloxacillin was stopped on day 14. Mr A remained well. Urine microscopy showed:

- <10x10^6/L erythrocytes
- <10x10^6/L leucocytes, and
- + hyaline casts.

Renal ultrasound showed normal sized kidneys with no scars or hydronephrosis. Mr A's renal function started improving 4 days following the cessation of flucloxacillin. On day 18, his serum creatinine was 198 µmol/L, urea 12.8 mmol/L. By day 28, his renal function had entirely normalised, with a serum creatinine of 100 µmol/L and urea of 7.2 mmol/L.

The temporal relationship between the onset of acute renal failure and the initiation of flucloxacillin, and subsequently, the cessation of flucloxacillin and the normalisation of renal function, suggests a causative role of flucloxacillin in acute renal failure in this case. Flucloxacillin is significantly excreted renally.[1] Given Mr A's weight was 80.10 kg, with normal eGFR and serum creatinine on presentation, he received appropriate dosage of flucloxacillin.

In Mr A's case, a pre-renal cause of acute renal failure is unlikely. He remained euvolaemic during admission without any sign to suggest hypovolaemia, such as postural hypotension. A postrenal cause is excluded by an unremarkable renal tract ultrasound, without prostatomegaly or hydronephrosis. Another possibility is sepsis. However, Mr A was systemically well. His joint aspirate, blood and urine cultures were negative. Given the time course association with the use of flucloxacillin, the most likely mechanism of action is flucloxacillin induced acute interstitial nephritis. Flucloxacillin

has several other well known adverse effects, including hepatitis, gastrointestinal upset and hypersensitivity reactions.[1] These were not relevant in Mr A's case.

Acute interstitial nephritis

Acute interstitial nephritis (AIN) is an important cause of acute renal failure.[2,3] Histological features are interstitial oedema and an interstitial infiltrate consisting of T lymphocytes and monocytes.[2] Drug induced AIN is the most common form of AIN. Acute interstitial nephritis may also be secondary to infection and autoimmune disorders.

Drugs commonly implicated in AIN include:

- penicillins
- cephalosporins, and
- nonsteroidal anti-inflammatory drugs (NSAIDs).

In drug induced AIN, acute renal impairment is temporally related to the inciting drug. Renal impairment occurs within 3 weeks of starting the drug in 80% of patients.[3] Most patients present with nonspecific symptoms.

Flucloxacillin induced AIN

A literature search was performed using Medline (1950 to present) and EMBASE (1980 to present). Using Medline, searches were done on the topics: flucloxacillin, nephritis, kidney diseases. These terms were mapped to medical subject headings (MeSHs) and exploded to include related terms. Results of the searches were combined and yielded 10 results: four irrelevant; four review articles; and two case reports discussed flucloxacillin induced AIN. The search parameters were: MeSH Heading:exp=floxacillin AND (Topic=nephritis OR MeSH Heading:exp=Nephritis OR MeSH Heading:exp=Kidney Diseases). A second search using EMBASE on flucloxacillin/adverse drug reaction and interstitial nephritis/nephritis produced the same results.

Westberg and Bjork[4] described a case of AIN in a patient with *Staphylococcal aureus* sepsis who was treated with flucloxacillin. The compounding factors were concurrent sepsis and the administration of frusemide and cloxacillin. All these factors could cause AIN.

Bakker et al[5] described a case of AIN in a patient with aortic valve replacement who received flucloxacillin at a total dose of 4 g/day intravenously, prophylactically following drainage of haemarthrosis.[5] The patient became unwell, and the serum creatinine eventually rose to 748 µmol/L before renal biopsy confirmed the diagnosis. Prednisolone was initiated at that stage, with significant improvement in renal function over 12 days.

Management of drug induced AIN

The mainstay of therapy is cessation of the suspected offending drug.[2,3,6] This is often successful. No further investigation or therapy is required if a patient's renal function showed improvement within 1 week following drug cessation.[6] Buysen et al[7] showed in a study of 27 patients with biopsy proven AIN, that renal function normalised in 17 patients with conservative measures.

Given that our case study Mr A was asymptomatic, and his renal function rapidly improved following cessation of flucloxacillin, conservative management of his acute renal failure was justified.

Indications for renal biopsy

The diagnosis of AIN can only be made on renal biopsy. It needs to be considered if:

- renal function does not improve within 1 week of drug cessation
- severe acute renal failure (eg. serum creatinine >300 µmol/L)
- diagnosis is uncertain.

When to use corticosteroids

There are no randomised controlled trials on corticosteroid treatment of AIN. The available data is conflicting. The authors analysed the two largest, recent retrospective studies.

Study 1

Clarkson et al[8] retrospectively analysed 60 cases of biopsy proven AIN over a 12 year period at one institution, of which 92% were drug induced. All patients 15 years or over with biopsy proven AIN were included. Exclusion criteria were presence of pyelonephritis, connective tissue disorder or sarcoidosis. The aetiological factors were NSAIDs (44%), antibiotics (33%) and proton pump inhibitors (7%). Forty-two patients had complete follow up. Corticosteroid was given in 60% of these cases. The decision to use corticosteroid was made by the treating nephrologist. The typical steroid regimen was: methylprednisolone 500 mg IV for 2–4 days followed by oral prednisolone 0.75 mg/kg tapered over 3–6 weeks. Mean serum creatinine in the corticosteroid group was 700 µmol/L vs. 545 µmol/L in the conservative group. The outcome measure was serum creatinine. There was no statistically significant difference at 1, 6 and 12 months. Mean final serum creatinine at 12 months in the corticosteroid group was 144 µmol/L vs. 141 µmol/L in the conservative group.

Study 2

Gonzalez et al[9] retrospectively analysed 61 cases of biopsy proven AIN in this multicentre study over a 31 year period, of which 52 cases were treated with steroids. Patients with systemic diseases were excluded. The aetiological factors were antibiotics (56%), NSAIDs (37%) and other drugs. The typical steroid regimen was: IV methylprednisolone 250–500 mg/day for 3–4 days followed by oral prednisolone 1 mg/kg tapered over 8–12 weeks. Mean serum creatinine in the corticosteroid group was 531 µmol/L vs. 441 µmol/L in the conservative group. The outcome measure was serum creatinine. Patients in the corticosteroid group had significantly lower mean final serum creatinine (189 µmol/L) than patients in the conservative group (333 µmol/L). The mean period of follow up was 19 months in the corticosteroid group versus 18 months in the conservative group. A delay in initiation of

corticosteroid following drug cessation was statistically significantly related to higher serum creatinine.

In the absence of definitive data, expert review recommends a renal biopsy to confirm the diagnosis of AIN before considering a trial of corticosteroids if there is no significant improvement in renal function within 1 week of drug cessation.[3,6] However, some nephrologists consider the risk of renal biopsy at 1 week too high. Therefore, if the patient's renal function does not improve within 1 week, it is reasonable to refer to a nephrologist who will then assess the patient's suitability for renal biopsy. An empirical trial of corticosteroids may be reasonable in patients highly suspected of drug induced AIN on clinical assessment who are unsuitable for renal biopsy (eg. coagulopathy).

Conclusion

The safe use of flucloxacillin requires careful consideration of its adverse effect profile. Flucloxacillin induced acute renal failure due to interstitial nephritis can be managed conservatively. In patients whose renal function does not improve within 7 days, referral should be made to a nephrologist, with consideration given to obtaining the diagnosis by renal biopsy, followed by possible corticosteroid therapy.

Conflict of interest: none declared.

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