Lesson of the month 2: An easily missed cause of confusion

Authors: Ben Oliveira,[A] Sangita Chaterjee[B] and Aine Burns[C]

ABSTRACT

We describe the case of an 85-year-old woman who developed acute confusion, acute kidney injury and temperature spikes while on extended courses of beta-lactams for osteomyelitis. The cause of her deterioration was felt to be due to sepsis when in fact it was as a result of toxicity from antibiotics. This was demonstrated by a rapid resolution in her condition following haemodialysis. We also performed a literature review to appraise the neuro- and nephrotoxicity of various antibiotics and how best to manage toxicity when it occurs.

KEYWORDS: Acute kidney injury, AKI, beta-lactams, dialysis, encephalopathy, toxicity

Case history

In September 2015, a fully lucid 85-year-old woman with type 2 diabetes, hypertension, peripheral vascular disease and previous right above knee amputation was admitted under the vascular team with an ischaemic, infected left foot. C-reactive protein and white blood cell count were 61 mg/L and 4.3×10^9, respectively. Augmentin was started and on day 3 of the admission, after failed angioplasty, she underwent a trans-metatarsal amputation. Following the surgery, on the basis of culture results, she was switched to intravenous ceftazidime 2 g three times a day with a plan to continue for 6 weeks. However, 1 month into her hospital stay her creatinine rose above 100 µmol/L (previously 57 µmol/L) and by the end of October it had increased further to 210 µmol/L. Coincident with the rise in creatinine she became confused and febrile. Urinalysis, microscopy and cultures revealed 2+ of protein with no evidence of urine infection. She had normal sized kidneys with preserved cortico-medullary differentiation on ultrasound examination. Unenhanced computed tomography scan of the head was normal. C-reactive protein and white blood cell count were 24 mg/L (normal <5 mg/L) and 14.61×10^9 (normal range: $3.5–11\times10^9$), respectively, at this point but were trending downwards (Fig 1). The stump was clean and healing well. However, she continued to spike temperatures of up to 39°C that persisted for several days and prompted the addition of amoxicillin and then later temocillin and meropenem for presumed pneumonia despite no hypoxia and normal chest X-ray.

Her condition continued to worsen with her creatinine climbing to 350 µmol/L. Her Glasgow Coma Scale (GCS) score had deteriorated to 5/15 (E1, M3 V1). Muscle tone was normal throughout but occasional myoclonic jerks were observed bilaterally. Corneal reflexes and dolls eye movements were present. At this point, her general deterioration was deemed to be most likely a result of uncontrolled sepsis. However, an electroencephalogram (EEG) showed brain wave patterns suggestive of non-convulsive status epilepticus (NCSE). The possibility of beta-lactam toxicity was raised by the consulting nephrology team. Antibiotics were stopped and the patient underwent four sessions of haemodialysis. There was a steady and dramatic improvement in her GCS score and renal function (Fig 1).

Discussion

Several of this patient's symptoms, particularly the swinging fevers, led those caring for her to believe that her deterioration was due to ongoing sepsis. While beta-lactam neurotoxicity is relatively well recognised it was overlooked in this clinical setting until quite late in the course of her illness. This case highlights several learning points of interest to all those involved in caring for patients receiving antibiotics.

The effects of beta-lactams on the central nervous system (CNS) have been known since the 1940s when classic experiments by Walker *et al* on macaque monkeys showed that injecting penicillin into their cerebral cortex left them listless and uninterested in their surroundings.[1] In humans, the clinical manifestations of toxicity include confusion, disorientation, twitching, somnolence, myoclonus and convulsions.[2,3] The mechanism of action of beta-lactam neurotoxicity is thought to be the antagonistic action of the beta-lactam ring on the GABA receptor in the brain. As GABA is the main inhibitory neurotransmitter in the brain, its inhibition results in CNS excitation and seizures. Cephalosporins, like penicillins, contain a beta-lactam ring and are thus also associated with neurotoxicity.[4] Among the cephalosporins, ceftazidime is considered to be particularly prone to causing CNS disturbances.[5] In one series, the incidence of seizures with ceftazidime was reported to be as high as 3 in 1,000 patients.[6] The mean daily dose for those developing neurotoxicity was 4 g and EEG evidence of NCSE

Authors: [A]specialty registrar in general and renal medicine, Royal Free Hospital, London, UK; [B]foundation training year 1 doctor, Royal Free Hospital, London, UK; [C]consultant nephrologist and director of postgraduate medical education, Royal Free Hospital, London, UK

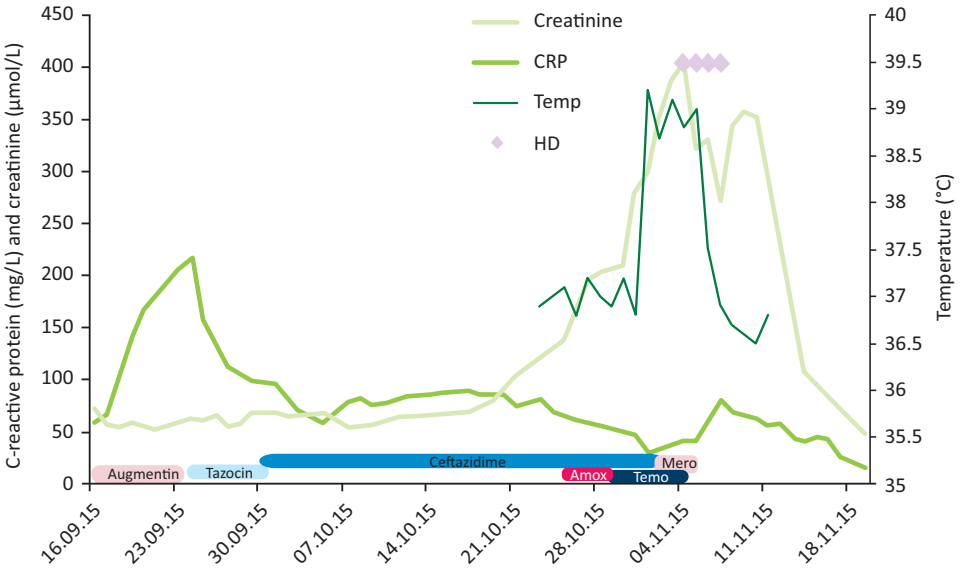

Fig 1. Blood test results and patient's temperature over time. Antibiotic courses are displayed in solid bars at the bottom of the graph. Amox = amoxicillin; CRP = C-reactive protein; HD = haemodialysis session; Mero = meropenem; Temo = temocillin; Temp = temperature.

was found in 75% of patients where it was performed.[6] Myoclonus was reported in 50%. Background renal dysfunction and prior CNS lesions are known to add to the risk of antibiotic induced seizures.[7,8] The time to developing encephalopathy from starting a cephalosporin has been reported as between 1 and 10 days.[9] Our patient had been on ceftazidime for nearly 1 month before any confusion was noted. However, once she developed renal dysfunction the confusion ensued very quickly. Ceftazidime is exclusively renally excreted and the half-life of the drug increases significantly as glomerular filtration rate (GFR) decreases.[10] This patient's ceftazidime dose was not decreased as she developed acute kidney injury and thus it is likely increased drug levels resulted in or exacerbated the CNS toxicity.

Some beta-lactams are known to be directly nephrotoxic causing acute tubular necrosis affecting the proximal tubule, particularly if intracellular drug concentrations are high.[11] Cephaloridine is actively transported into the proximal tubular cells via the baso-lateral membrane and there is little secretion into the lumen on the apical side, which results in high intracellular concentrations; this puts it among the most nephrotoxic beta-lactams.[11] Ceftazidime on the other hand does not accumulate in tubular luminal cells in high concentrations and thus is not traditionally associated with nephrotoxicity. Even so, clinical studies have shown that ceftazidime can in fact result in renal impairment. In one study, the authors showed that GFR, as measured by EDTA clearance, fell by a mean of 9.6 mL/min during treatment with ceftazidime despite serum creatinine remaining unchanged. In the group of patients with estimated GFR of less than 30 mL/ min at the start of therapy, the effects on kidney function were even more pronounced.[12] Another study has shown that the incidence of acute kidney injury increases with the number of potentially nephrotoxic drugs a patient is exposed to, and our patient had several courses of antibiotics that may have cumulatively worsened the toxic effects.[13] It is also possible that intravenous contrast administered in the first days of her admission during attempts to salvage the limb contributed to her renal dysfunction but the timing of the acute kidney injury would not support this.[14] Finally, this patient had nominally normal kidney function on admission but had had a previous above knee amputation so had reduced muscle mass. Thus, her estimated GFR may have overestimated her true kidney function and belied her risk of developing renal toxicity with ceftazidime. Acute interstitial nephritis has also been reported with ceftazidime but there was little evidence for this with no rash or eosinophilia and a quick recovery following dialysis (albeit with concomitant drug cessation).[15]

Swinging temperatures are also a well-recognised feature of beta-lactam drugs.[16] The timing of onset of the fevers related to beta-lactams has been reported at a median of 8 days after starting the offending drug but can occur after weeks to several months later.[16] As in this case, drug fever can result in clinical confusion. The inflammatory markers were only modestly elevated and were declining (Fig 1) despite the very high spiking temperatures and there was no convincing source of sepsis. Thus, in retrospect, the picture was much more typical of drug toxicity.

Grill and Maganti have suggested that EEG may be useful in detecting drug-induced NCSE in patients developing encephalopathy on potentially neurotoxic medications.[5] The finding of NCSE should prompt the immediate cessation of any possible offending drug and anti-epileptic medications may be required, at least temporarily. In normal renal function, stopping the cephalosporin should bring about resolution of encephalopathy in 2–7 days; however, Grill and Maganti still recommend that haemodialysis or hemofiltration be considered in those who have renal impairment.[5] A number of factors determine how dialysable any particular drug is, including the degree of protein binding and molecular weight.[17] Only the unbound fraction is available for diffusion across dialysis membranes. As the molecular weight of a drug increases, diffusion of the drug across a membrane progressively decreases; this means that large drugs like vancomycin are relatively poorly removed by dialysis.[18] Ceftazidime, which has

a relatively low molecular weight of 636.6 Daltons and is 90% unbounded, is very effectively removed by dialysis.[19]

This case serves to remind clinicians of the potentially toxic effects of beta-lactam antibiotics, especially in the context of renal failure. It also highlights that not all fevers are caused by infection but can be a consequence of the antibiotics used to treat them. Further, it demonstrates why a deteriorating patient, even in the presence of improving markers of infection, should prompt consideration of drug toxicity. Beta-lactam toxicity can be treated very effectively by withholding the drug and, if appropriate, initiating intensive haemodialysis. Extreme vigilance is important when prescribing antibiotics and dose adjustments are imperative when chronic kidney disease is present or acute kidney injury has occurred.

Key points

- Risk factors for beta-lactam neurotoxicity include renal impairment and prior CNS lesions.
- Swinging fevers can be a feature of beta-lactam toxicity occurring a median of 8 days after starting the drug.
- Development of acute kidney injury in a patient on beta-lactams should prompt consideration of dose reduction to prevent toxicity.
- EEG can be useful to detect NCSE in patients suspected of having drug-induced encephalopathy.
- The finding of beta-lactam induced encephalopathy should prompt immediate cessation of the offending drug and consideration of haemodialysis. ■

Conflicts of interests

All authors have no conflicts of interest to declare.

Acknowledgements

We would like to acknowledge Mr Sean Matheiken, Consultant Vascular Surgeon, for his contribution in the management of this case.

Written informed consent was obtained from the patient to publish the clinical details and images in this article.

References

1 Walker AE, Johnson HC, Kollros JJ. Penicillin convulsions; the convulsive effects of penicillin applied to the cerebral cortex of monkey and man. *Surg Gynecol Obstet* 1945;81:692–701.
2 Chow KM, Szeto CC, Hui ACF, Wong TYH, Li PKT. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacother J Hum Pharmacol Drug Ther* 2003;23:369–73.
3 Penicillin, ceftazidime, and the epilepsies. *The Lancet* 1992;340:400–1.
4 Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. *Ann Pharmacother* 2008;42:1843–50.
5 Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. *Br J Clin Pharmacol* 2011;72:381–93.
6 World Health Organization. *WHO Drug Information*. Volume 17, Number 2. Geneva: WHO, 2003:93–4.
7 Calandra G, Lydick E, Carrigan J, Weiss L, Guess H. Factors predisposing to seizures in seriously ill infected patients receiving antibiotics: experience with imipenem/cilastatin. *Am J Med* 1988;84:911–8.
8 Martínez-Rodríguez JE, Barriga FJ, Santamaria J *et al.* Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. *Am J Med* 2001;111:115–9.
9 Dakdouki GK, Al-Awar GN. Cefepime-induced encephalopathy. *Int J Infect Dis* 2004;8:59–61.
10 Leroy A, Leguy F, Borsa F *et al.* Pharmacokinetics of ceftazidime in normal and uremic subjects. *Antimicrob Agents Chemother* 1984;25:638–42.
11 Tune BM. Nephrotoxicity of beta-lactam antibiotics: mechanisms and strategies for prevention. *Pediatr Nephrol* 2014;11:768–72.
12 Alestig K, Trollfors B, Andersson R *et al* Ceftazidime and renal function. *J Antimicrob Chemother* 1984;13:177–81.
13 Moffett BS, Goldstein SL. acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. *Clin J Am Soc Nephrol* 2011;6;856–63.
14 Teruel JL, Marcén R, Onaindia JM *et al* Renal function impairment caused by intravenous urography: a prospective study. *Arch Intern Med* 1981;141:1271–4.
15 Ladagnous JF, Rousseau JM, Gaucher A, Saïssy JM, Pitti R. [Acute interstitial nephritis. Role of ceftazidime]. *Ann Fr Anesthèsie Rèanimation* 1996;15:677–80.
16 Mackowiak PA. Drug fever: mechanisms, maxims and misconceptions. *J Med Sci* 1987;294:275–96.
17 Parker PR, Parker WA. Pharmacokinetic considerations in the haemodialysis of drugs. *J Clin Hosp Pharm* 1982;7:87–99.
18 De Bock V, Verbeelen D, Maes V, Sennesael J. Pharmacokinetics of vancomycin in patients undergoing haemodialysis and haemofiltration. *Nephrol Dial Transplant* 1989;4:635–9.
19 Drugs.com. Ceftazidime – FDA prescribing information, side effects and uses. Available online at http://www.drugs.com/pro/ceftazidime.html [Accessed 12 July 2016].

Address for correspondence: Dr B Oliveira, Department of Renal Medicine, Royal Free Hospital, Hampstead, London NW3 2QG, UK.
Email: benoliveira@nhs.net