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Ceftriaxone-induced Encephalopathy: A Pharmacokinetic Approach

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ABSTRACT

We report a case of ceftriaxone-induced encephalopathy correlated with a high concentration of the drug in cerebrospinal fluid (CSF). Cephalosporin neurotoxicity is increasingly reported, especially in association with fourth-generation cephalosporins. The factors influencing CSF concentration are plasma concentration, liposolubility, ionization, molecular weight, protein binding and efflux. In our patient, high levels of ceftriaxone (27.9 mg/l) were found in CSF. β-Lactam-associated neurotoxicity is mainly due to similarities between GABA and the β-lactam ring. Because of differences in CSF/plasma ratios and blood–brain barrier efflux among patients, plasma drug monitoring cannot be used to estimate CSF concentration. As far as we know, this is the first reported case of ceftriaxone-induced encephalopathy associated with a high CSF concentration.

LEARNING POINTS

- Ceftriaxone dose adjustment and clinical surveillance are strongly recommended in patients with renal failure.
- Measuring ceftriaxone cerebrospinal fluid concentration could be useful for confirming ceftriaxone-induced encephalopathy.

KEYWORDS

Encephalopathy, ceftriaxone, cerebrospinal fluid (CSF) concentration

CASE DESCRIPTION

A 64-year-old man was admitted to our hospital for acute endocarditis. His past medical history was relevant for NASH-related cirrhosis complicated by hepatocarcinoma (for which he underwent partial hepatectomy after chemoembolization and subsequently radiotherapy and chemotherapy), type 2 diabetes, NSTEMI treated by PTCA and stenting, mild renal chronic insufficiency (MDRD 37 ml/min) and hypertension. He was receiving treatment with bisoprolol, simvastatin, ticagrelor, bumetanide, valsartan and acetylsalicylic acid.

Upon hospitalization, he was administered empirical antibiotic therapy with flucloxacillin, ampicillin and gentamicin. On day 6 of hospital admission, an echocardiogram revealed significant mitral vegetation with an associated aortic abscess which necessitated surgery with mitral and aortic valve replacement. The surgery was successful but the patient developed atrioventricular block which required external pacing. On day 11, as valve and blood cultures were negative, flucloxacillin was replaced with ceftriaxone (2 g twice a day). On day 15, the patient presented acute pericardial effusion associated with bilateral pleural effusion requiring surgical pericardiocentesis and pleural drainage. The clinical course was marked by cardiogenic shock requiring inotropes and vasopressors. He also needed continuous haemofiltration as he presented massive fluid overload and anuric renal failure.

On day 17, a definitive pacemaker was implanted since the atrioventricular block had not resolved. Evolution was favourable so sympathomimetic drugs and mechanical ventilation were stopped. The patient's neurological status was described as normal with only minor cognitive abnormalities (slow thinking and speech), which was attributed to his long hospitalization and complications. Continuous haemofiltration was switched to intermittent haemodialysis and he was discharged from the intensive care unit on day 23.

Ten days after his transfer to a standard ward, the patient was readmitted to ICU for acute encephalopathy. The neurological examination showed no focal deficits. The chemistry panel showed normal electrolytes, liver function and thyroid tests, and normal ammonaemia. No new drugs had been administered and the cerebral CT scan was normal. The investigations were completed by an EEG which showed toxic encephalopathy without epileptiform discharges. A lumbar puncture was performed and was normal. Since renal failure persisted and ceftriaxone 2 g twice a day had been continued, ceftriaxone-induced encephalopathy was suspected. Ceftriaxone CSF concentrations were high at 27.9 mg/l so the drug was discontinued. The patient recovered his neurological status 3 days after ceftriaxone cessation and without any further medical intervention. He was discharged from hospital 10 days later with no neurological sequelae.

DISCUSSION

Cephalosporin neurotoxicity is increasingly reported, especially in relation to fourth-generation cephalosporins [1]. By 2012, only eight cases of ceftriaxone-associated encephalopathy had been reported [2]. However, its real incidence is probably higher because it may be underdiagnosed, particularly if intoxication is mild and there are other possibly confounding factors.

Renal insufficiency is usually described in cases of ceftriaxone-induced encephalopathy, and so seems to be the main risk factor for this condition. However, the manufacturer states there is no need for ceftriaxone dose adjustment in renal impairment. Also, ceftriaxone is a non-dialyzable drug. Moreover, patients with renal impairment do not systematically present neurological complications associated with ceftriaxone. Mild hepatic impairment requires dosage adjustment only if there is coexisting renal failure. The adjusted dose is empirical and clinical surveillance of tolerance is strongly recommended.

It is difficult to predict ceftriaxone neurotoxicity, but pharmacokinetics may be helpful [3, 4]. The factors influencing the CSF concentration of ceftriaxone are plasma concentration, liposolubility, ionization, molecular weight, protein binding and efflux.

Plasma concentration is influenced by the dose and elimination of the drug, and also by the volume of distribution (Vd). Like all β-lactams, ceftriaxone is a hydrophilic antibiotic that, in normal state, has a low Vd and minor intracellular penetration. However, in pathological situations, Vd can dramatically increase, thus reducing plasma concentration. Approximately half of ceftriaxone is excreted, unchanged, in the urine, while the liver eliminates the remainder. In contrast to other β-lactams, ceftriaxone has a long half-life of 5–10 h, which is less influenced by renal dysfunction. Nevertheless, its clearance is significantly increased and membrane dependent during continuous haemofiltration [5]. Our patient received 2 g of ceftriaxone twice a day (in the context of endocarditis) for more than 20 days. Excessive plasma concentrations were probably reached because of the renal and fluctuating hepatic impairment. Nevertheless, at the beginning, our patient probably had a very high Vd (due to continuous haemofiltration, oedema, post-operative status, hypoalbuminaemia, drained pleural effusion and ascites) and concentrations probably remained low in plasma. As the patient recovered, Vd likely returned to normal values and plasma concentrations increased.

The molecular weight of ceftriaxone (554.58 g/mol) means it can easily penetrate the CSF (which is only possible if the molecular weight is below 800). However, because of low lipophilicity and low ionization, it diffuses poorly through the blood–brain barrier (BBB). Some pathological states including sepsis [6, 7] alter the permeability of the BBB. Recent research has shown significant changes in BBB diffusion in cirrhosis and hepatic failure [8]. Despite low penetration of ceftriaxone in the CSF of healthy subjects, cirrhosis may be associated with high levels of some molecules crossing from the plasma to the brain. This could adversely affect the condition of the patient.

Protein binding is also a crucial parameter since only the free fraction of a drug is able to pass through the BBB. Compared with other antibiotics, ceftriaxone has high affinity for plasma protein, with 90% of ceftriaxone bound to protein in the plasma of healthy subjects. The free fraction strongly increases as protein concentration reduces, as in cirrhosis and fluid overload, leading to higher CSF penetration. The protein binding of ceftriaxone in the CSF must also be taken into account when considering toxic or therapeutic effects on the brain. Theoretically, since the protein concentration in CSF is generally low compared to that in plasma (100 times less), the impact on the free fraction is thought to be negligible. However, although this may be true for most antibiotics with high BBB penetration, it may not be for ceftriaxone. At steady state, the plasma/CSF protein ratio ranges from 40 to 100 in healthy patients [9]. The effect of a pathological CSF protein level on the free fraction of ceftriaxone in the brain is not known, nor is the therapeutic/toxic effect. Our patient had mildly elevated protein in the CSF that, in theory, would not protect him from toxic levels.

Efflux involves membrane transport proteins at the BBB which actively remove drugs from the brain, including antibiotics [10]. The resulting effect on the CSF concentration of a drug is unpredictable. Polymorphisms of P-glycoprotein (also called MDR1 protein) leading to variable drug transport activity with potential effects on outcomes/therapeutic failure or adverse drug events have been demonstrated [11].

These proteins can also undergo induction or inhibition by many drugs, thus modulating their activity. For example, common medications such as atorvastatin, clarithromycin and verapamil are MDR1 inhibitors with an undemonstrated effect on CSF drug concentration [12,13].
Finally, despite the absence of a clear temporal link between the initiation of ceftriaxone and symptoms of encephalopathy in our patient, the diagnosis was clear. The delay could have been due to two factors. First, as discussed above, large variations in Vd (for instance due to continuous haemofiltration [14]) could temporarily reduce the large dose of ceftriaxone initially prescribed. Second, once Vd had normalized and continuous haemofiltration had ceased, concentrations started to increase. Time is required for ceftriaxone to reach maximal (and probably toxic) levels in CSF because it diffuses slowly across the BBB as a hydrophilic drug. Consequently, a high level of ceftriaxone was demonstrated in CSF after lumbar puncture (27.9 mg/l) by high-performance liquid chromatography with photodiode array detection (HPLC-DAD). The reference values in healthy subjects administered 2 g twice daily range from 2 to 7 mg/l [14, 15]. In patients with meningitis, the penetration rate through the inflamed BBB is likely higher. However, a study of 17 adults with meningitis showed considerable differences in ceftriaxone CSF concentration, ranging from 0.85 to 18.29 mg/l (median 3.44 mg/l) [16]. In a paediatric population with meningitis, a study showed C3 concentrations in CSF ranged from 0.7 to 8.3 mg/l [17].
β-Lactam-associated neurotoxicity is mainly due to similarities between GABA and the β-lactam ring. Cephalosporin exerts competitive GABA receptor inhibition, leading to a decrease in GABA release and inhibitory neurotransmission [18]. In 2016, an extensive literature review of antibiotic-associated encephalopathy found cephalosporin and penicillin neurotoxicity had a similar clinical pattern [19]. This clinical phenotype, namely type I AAE (antibiotic-associated encephalopathy), generally consisted of myoclonus or seizure with normal EEG and MRI. This suggests the possibility of an identical toxic mechanism through β-lactam molecules. Based on a study of 30 patients with febrile neutropenia receiving cefepime, Rhodes et al. [20] found that a trough serum concentration of ≥22 mg/l predicted a 50% probability of neurotoxicity. However, in 2016 Lonsdale DO et al. [21] analysed this cut-off value and found it was not specific enough to predict toxicity. Furthermore, because of different CSF/plasma ratios and BBB efflux among patients, plasma drug monitoring probably cannot be used to estimate CSF concentration [22]. This highlights the potential utility of measuring CSF dosage for diagnosing neurotoxicity. Lamoth et al. described only two cases of cefepime-induced encephalopathy with reported CSF values (2.4 mg/l and 18 mg/l). These data are obviously insufficient for defining the CSF cut-off level associated with neurotoxicity and even less so for identifying a common threshold among all β-lactams. Cefepime, ceftazidime and ertapenem are the most frequent β-lactams associated with neurological adverse effects.

CONCLUSION

As far as we know, this is the first reported case of ceftriaxone-induced encephalopathy associated with a high CSF concentration of the drug. The literature indicates that this syndrome is quite rare, but ceftriaxone is a widely used antibiotic around the world. Moreover, since patients receiving ceftriaxone may be neurologically fragile (neurologic drugs, ICU admission, septic encephalopathy), this condition could be significantly misdiagnosed. Examining the pharmacokinetics can offer clues but not prevent the condition. Finally, as suggested by this case, measuring ceftriaxone CSF concentration could be useful for confirming the diagnosis, especially in the absence of other causes.

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