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Case Report

Cephalosporin-Related Neurotoxicity in a Ceftriaxone-Treated Critically Ill Child: A Case Report

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Keywords

Ceftriaxone · Encephalopathy · Therapeutic drug monitoring · Child

Abstract

Introduction: We describe a child with meningococcal sepsis who suffered cephalosporin-related neurotoxicity. ***Case Presentation:*** A four-year-old girl was treated with intravenous ceftriaxone and supportive therapy. After rapid improvement, inotropic and respiratory support was stopped within 2 days. However, she developed renal failure and, on day four, deteriorated neurologically. Research into the cause of her encephalopathy revealed supra-therapeutic ceftriaxone concentrations with greatly increased unbound fractions leading to the diagnosis of cephalosporin-related neurotoxicity. Ceftriaxone treatment was discontinued, and renal replacement therapy was initiated on day six. With both discontinuation of ceftriaxone and renal replacement therapy, the girl's condition improved rapidly. ***Conclusion:*** We postulate that in the described case both renal impairment and hypoalbuminemia played an important role in the development of high unbound ceftriaxone serum levels. We advocate therapeutic drug monitoring for ceftriaxone in critically ill children with renal failure or hypoalbuminemia.

Introduction

Ceftriaxone is a first-choice drug in empirical sepsis therapy in children [1] and recommended for children with community-acquired sepsis in many guidelines [2, 3]. High-dosing regiments are well tolerated and effective for the treatment of serious infections,

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including meningitis [4, 5]. However, serious side effects of ceftriaxone, such as encephalopathy, related to excessively high serum levels have recently been reported in adult and elderly patients on normal dosing regiments [6, 7].

Ceftriaxone clearance is dependent on biliary and renal excretion [8] and has a long half-life due to its high albumin-binding capacity [9]. These pharmacokinetic parameters have been known to change in critically ill patients [10], resulting in abnormal plasma concentrations of ceftriaxone [11].

These factors combined should prompt clinicians to consider monitoring ceftriaxone exposure in critically ill children, especially after unexpected changes in neurological status and in case of developing renal failure or severe hypoalbuminemia. Potentially due to the relative novelty and low incidence of some of these findings, recommendations regarding therapeutic drug monitoring (TDM) for ceftriaxone are lacking. The following case advocates for TDM in critically ill children. Awareness of ceftriaxone toxicity is especially relevant considering its widespread use.

Case Report

Present History

A four-year-old girl with an unremarkable medical history was referred to the pediatric intensive care unit for meningococcal sepsis. She had been ill for half a day prior to admission with symptoms of fever, vomiting, and rapid development of petechiae and purpura.

Physical Examination

The patient was tachypneic, tachycardic, and pale colored with cold extremities. Her heart rate was 170 beats per minute, she had a mean arterial blood pressure of 60 mm Hg, and she had a respiratory rate of 40 breaths per minute. Laboratory results showed a respiratory-compensated metabolic acidosis, thrombocytopenia, and prolonged clotting tests (Table 1).

Initial Resuscitation

She was given fluid resuscitation (40 mL/kg), ceftriaxone 100 mg/kg once daily, 2 L/min nasal oxygen, dobutamine (5 μg/kg/min), and low-dose noradrenaline (0.05 μg/kg/min). Fresh frozen plasma was administered for consumption coagulopathy. Her circulatory condition stabilized shortly thereafter, allowing inotropic and respiratory support to be discontinued after 48 h. She had become oliguric after admission, her blood urea and creatinine rose, and the renal failure was attributed to the preceding shock. Renal replacement therapy was not initiated because her overall clinical condition had improved and absolute indications (metabolic or fluid overload) were lacking. Blood culture confirmed a ceftriaxone-susceptible *Neisseria meningitidis*.

Clinical Course

From the fourth day of admission onward, she showed an altered state of consciousness with marked drowsiness and incoherent speech. This was in clear contrast to her mental state in the previous days when she was able to communicate with her parents and caregivers. During formal neurological examination, she opened her eyes in response to pain, actively resisted passive movement of all the limbs, and uttered sounds. Neither myoclonus nor focal abnormalities were observed.

Table 1. Laboratory values at admission and during encephalopathy

Admission			4th day		
pH	7.36		pH	7.36	
pCO_2	3.1	kPa	pCO_2	4.5	kPa
Bicarbonate	13	mM	Bicarbonate	19.3	mM
Lactate	9.9	mM	Lactate	1.2	mM
Hb	5.9	mM	Hb	4.9	mM
Thrombocytes	58	$*10^9$/L	Ca^{2+}	1.1	mM
Leucocytes	3.4	$*10^9$/L	Mg	1.09	mM
CRP	55	mg/L	Cl	103	mM
APTT	74	s	Na	133	mM
PT-INR	2.2		K	4.6	mM
Fibrinogen	1.5	g/L	Phosphate	1.49	mM
Factor V	0.22	µ/mL	Ammonia	15	µM
D-Dimer	35.2	mg/L	Albumin	21	g/L
			Bilirubin	6	µM
			ASAT	90	µ/L
			ALAT	188	µ/L
			LDH	2,441	µ/L
			CK	66	µ/L
			Urea	21	mM
			Creatinine	355	µM

Hb, hemoglobin; CRP, c-reactive protein; APTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase.

Investigations

To rule out a cerebrovascular cause or hydrocephalus for the altered mental state, a CT scan of the brain was performed, which revealed no signs of abnormalities. After psychiatric evaluation, delirium was considered unlikely due to the lack of characteristic symptoms such as fluctuation in consciousness or hallucinatory behavior.

Taking the preceding period of critical illness and renal failure into account, "metabolic encephalopathy" became the working diagnosis. Whether renal failure was the predominant cause for the encephalopathy was doubtful, given the moderately elevated urea of 22.8 mmol/L at the onset of symptoms. Therefore, other causes for an encephalopathy were considered. Apart from the known elevated urea and creatinine, laboratory testing revealed no other significant abnormalities (shown in Table 1).

Potential side effects of administered drugs were reviewed. Since sedatives and analgesics other than paracetamol had scarcely been administered, and none of them continuously, we considered cephalosporin-related neurotoxicity (CRN). CRN was particularly suspected because of the renal failure and hypoalbuminemia, and thus potentially increased risk of high unbound ceftriaxone exposure. Measurement of serum levels of ceftriaxone on day five revealed elevated total and unbound trough concentrations (130 and 33.9 mg/L, respectively), well above the cut-off value for dose reduction (>10x MIC). The free fraction was

also elevated 26.1% (reference 4–17%) [12]. On day 6 of ceftriaxone therapy, the free fraction increased even further to 42.5%. Hence, CRN was considered the likely cause of her altered mental state.

Treatment

As soon as CRN was considered a possible cause for the encephalopathy, ceftriaxone administration was switched from once daily dosing to continuous infusion to avoid high peak exposure. When the laboratory results of the ceftriaxone blood levels returned on day 6, its administration was discontinued completely, and she had completed the protocolled treatment course for meningococcal sepsis at this point [2]. Concurrent with these changes, continuous venovenous hemofiltration was initiated as renal recovery was considered too slow with metabolic deterioration (potassium 5.8 mmol/L, urea 36.3 mmol/L) and the development of fluid overload.

After discontinuation of ceftriaxone and initiation of continuous venovenous hemofiltration, the girl's mental status improved markedly in the following 2 days (Fig. 1). Renal function recovered during the following weeks, initially with increasing urine output, followed by improved clearance.

The patient was transferred from the pediatric intensive care unit to the pediatric ward after 14 days, where treatment for the sequelae of meningococcal sepsis (skin infection) and acute renal failure (hypertension, hyperphosphatemia) was continued. She was discharged after 30 days of admission and remains in long-term follow-up. At 1 year after the admission, her estimated glomerular filtration rate was 109 mL/min/1.73 m^2 with mild proteinuria. Due to fatigue, she was able to attend 4 out of 5 school days. The CARE Checklist for this case report is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534890).

Discussion

CRN has been described in both adults and [13, 14]. CRN can be caused by different cephalosporins, including ceftriaxone [6, 14]. In a pharmacovigilance study investigating CRN, ceftriaxone was the second most frequent drug associated with CRN, cefepime being the most frequent [6]. CRN symptoms vary from confusion, agitation, hallucinations, myoclonus, seizures, tremor to coma [7]. Usually, CRN resolves within days after cephalosporin withdrawal [6, 7].

In patients with suspected CRN, cephalosporin serum levels are often elevated. In the pharmacovigilance study, 90% of the measured cases were above the therapeutic range [6]. A total ceftriaxone trough plasma concentration above 100 mg/L is associated with neurological adverse drug reactions in high-dose ceftriaxone regiments [15]. In most studies, solely the total concentration of ceftriaxone is reported. However, the plasma unbound concentration might correlate better with a risk for the development of adverse drug reaction, as this might better represent tissue levels of ceftriaxone concentration [16].

Ceftriaxone clearance can be markedly reduced in critically ill patients and has been shown to correlate with renal clearance [11, 17]. Interestingly, ceftriaxone to albumin binding in serum from patients with impaired renal function was shown to be decreased [11]. Accordingly, in critically ill patients the free fraction of ceftriaxone is elevated compared to healthy volunteers [11]. In the pharmacovigilance study investigating CRN, ceftriaxone-induced CRN was accompanied by renal impairment in half of the cases [6]. Interestingly, the aforementioned reported pediatric cases of CRN involved children on chronic peritoneal dialysis [13, 14].

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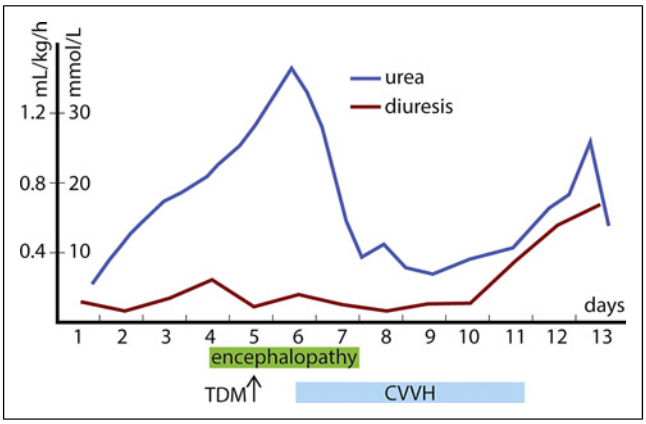

Fig. 1. Time course of diuresis, urea, and events during admission at PICU. Green bar represents the duration of encephalopathy. TDM, therapeutic drug monitoring; CVVH, continuous venovenous hemofiltration; PICU, pediatric intensive care unit.

Renal impairment thus appears to result in an increased total and – to an even stronger extent – unbound concentration of ceftriaxone. Although renal impairment is frequently present in cases of ceftriaxone CRN, serum albumin levels and levels of unbound ceftriaxone are infrequently reported. However, these might play an important yet under-recognized role in ceftriaxone toxicity and warrant further investigation.

Despite the wide use of ceftriaxone, there are a few reports on CRN in children. This raises the question of whether children are less frail than adults, noting that increased age is a risk factor for neurological side effects of high-dose ceftriaxone regiments [15]. On the other hand, CRN might go unrecognized as critically ill children usually suffer from multiple organ dysfunction and are often intubated and sedated. The patient presented here did not require respiratory support beyond low-flow oxygen and thus may have been the exception to the rule. We argue that when ceftriaxone TDM services are available, determining serum concentration may be helpful in preventing CRN in children with renal failure.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Parents have given written informed consent for publication of the details of their child's medical case and the accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

M. Sylva was involved in writing the case report. Alan Abdulla, Birgit Koch, and Jaap Mulder were involved in writing and redirecting the case report.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author. A protocol for the serum ceftriaxone measurement is available upon request.

References

1 Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign International Guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med. 2020;21(2):e52–106.
2 Stichting werkgroep antibiotica beleid. https://children.nl.antibiotica.app/.
3 The National Institute for Health and Care Excellence. Sepsis: recognition, diagnosis and early management.
4 Martin E, Koup JR, Paravicini U, Stoeckel K. Pharmacokinetics of ceftriaxone in neonates and infants with meningitis. J Pediatr. 1984;105(3):475–81.
5 Schaad UB, Suter S, Gianella-Borradori A, Pfenninger J, Auckenthaler R, Bernath O, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. N Engl J Med. 1990;322(3):141–7.
6 Lacroix C, Kheloufi F, Montastruc F, Bennis Y, Pizzoglio V, Micallef J. Serious central nervous system side effects of cephalosporins: a national analysis of serious reports registered in the French Pharmacovigilance Database. J Neurol Sci. 2019;398:196–201.
7 Triplett JD, Lawn ND, Chan J, Dunne JW. Cephalosporin-related neurotoxicity: metabolic encephalopathy or non-convulsive status epilepticus? J Clin Neurosci. 2019;67:163–6.
8 Patel IH, Chen S, Parsonnet M, Hackman MR, Brooks MA, Konikoff J, et al. Pharmacokinetics of ceftriaxone in humans. Antimicrob Agents Chemother. 1981;20(5):634–41.
9 McNamara PJ, Trueb V, Stoeckel K. Ceftriaxone binding to human serum albumin. Indirect displacement by probenecid and diazepam. Biochem Pharmacol. 1990;40(6):1247–53.
10 Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498–509.
11 Schleibinger M, Steinbach CL, Töpper C, Kratzer A, Liebchen U, Kees F, et al. Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients. Br J Clin Pharmacol. 2015;80(3):525–33.
12 Perry TR, Schentag JJ. Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. Clin Pharmacokinet. 2001;40(9):685–94.
13 Alpay H, Altun O, Biyikli NK. Cefepime-induced non-convulsive status epilepticus in a peritoneal dialysis patient. Pediatr Nephrol. 2004;19(4):445–7.
14 Chedrawi AK, Gharaybeh SI, Al-Ghwery SA, Al-Mohaimeed SA, Alshahwan SA. Cephalosporin-induced non-convulsive status epilepticus in a uremic child. Pediatr Neurol. 2004;30(2):135–9.
15 Le Turnier P, Navas D, Garot D, Guimard T, Bernard L, Tattevin P, et al. Tolerability of high-dose ceftriaxone in CNS infections: a prospective multicentre cohort study. J Antimicrob Chemother. 2019;74(4):1078–85.
16 Balant L, Dayer P, Auckenthaler R. Clinical pharmacokinetics of the third generation cephalosporins. Clin Pharmacokinet. 1985;10(2):101–43.
17 Leegwater E, Kraaijenbrink BVC, Moes D, Purmer IM, Wilms EB. Population pharmacokinetics of ceftriaxone administered as continuous or intermittent infusion in critically ill patients. J Antimicrob Chemother. 2020;75(6):1554–8.