Medicines Adverse Reactions Committee

Meeting date	2/12/2022	Agenda item	3.2.1
Title	**Cephalosporins and neurotoxicity**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Sponsor(s)**		
Cefalexin	Max Health Limited, Novartis New Zealand Limited, Boucher & Muir (New Zealand) t/a BNM Group		
Cefazolin	AFT Pharmaceuticals Ltd		
Cefuroxime	AFT Pharmaceuticals Ltd, GlaxoSmithKline NZ Limited		
Cefaclor	Douglas Pharmaceuticals Limited		
Cefotaxime	Pfizer New Zealand Limited		
Ceftriaxone	AFT Pharmaceuticals Ltd, Devatis Ltd		
Ceftazidime	AFT Pharmaceuticals Ltd, Fresenius Kabi New Zealand Limited		
Ceftazidime (combination)	Pfizer New Zealand Limited		
Cefepime	AFT Pharmaceuticals Ltd, Fresenius Kabi New Zealand Limited		
Ceftaroline fosamil	AstraZeneca Limited		
Ceftolozane (combination)	Merck Sharp & Dohme (New Zealand) Ltd		
PHARMAC funding	• Community: Cefazolin*, cefalexin, cefuroxime* (PO), cefaclor, ceftriaxone*. • Hospital: Cefazolin, cefalexin, cefuroxime (IV/PO), cefaclor, cefotaxime, ceftazidime*, ceftriaxone, cefepime*, ceftaroline fosamil* **when meets funding criteria.*		
Previous MARC meetings	The topic of cephalosporins and neurotoxicity adverse effects has not previously been discussed by the MARC. Cephalosporins and cross reactivity was discussed at the September 2015 and January 2016 MARC meetings.		
International action	FDA: Drug Safety Communication – cefepime and risk of seizure in patients not receiving dosage adjustments for kidney impairment (June 2012) Health Canada: Summary Safety review – ceftriaxone-containing products (March 2021) Health Canada: Cephalosporin and seizures safety review (in progress) TGA: Ceftriaxone and risk of hepatitis and encephalopathy (December 2021) PRAC: Ceftriaxone and encephalopathy (October 2020)		
Prescriber Update	No previous publications about this topic.		
Classification	Prescription medicine		
Usage data	See usage section.		

Advice sought	**The Committee is asked to advise:**
	• Whether there is evidence for an association between the entire cephalosporin class and neurotoxicity?
	  o If no, is there evidence for an association between a specific generation of cephalosporin and neurotoxicity, or
	  o Is there evidence for an association for a specific cephalosporin and neurotoxicity?
	
	• If there is evidence for an association (for the entire class, a specific generation, or a specific cephalosporin):
	  o Does the Committee consider that a warning should be included in section 4.4 for all products and related to neurotoxicity in general or specific separate warnings for encephalopathy and/or seizures
	  o If a warning is desirable, should it include risk factors, and management (for example EEG monitoring and discontinuation of treatment),
	  o Should these terms be included in section 4.8: encephalopathy, delirium, confusion, depressed level of consciousness, agitation, hallucinations, disorientation, tremor, myoclonus, seizures, NCSE.
	
	• The risk of neurotoxicity appears to be linked with renal function. An inconsistency in recommendations of renal dosing has been identified across countries. Does the Committee consider the inconsistences to be important and require adjustment.
	
	• Does the topic require further communication, other than MARC's remarks in Prescriber Update?

Table of Contents

1 PURPOSE

Medsafe was notified by a sponsor of a safety and effectiveness review initiated by Health Canada for the cephalosporin product class and the potential safety issues of seizures. The outcome of this review is not yet available.

The purpose of this paper is to review the information on cephalosporin-induced neurotoxicity. Antibiotics, including cephalosporins have be associated with such adverse effects, however there is limited information in the NZ data sheets.

2 BACKGROUND

2.1 Cephalosporins

Cephalosporins are a class of broad-spectrum antibiotics. They are used in the treatment of a range infections related to their bacterial susceptibility in community and hospital [1].

Cephalosporins are classified as beta-lactam antibiotics. Figure 1 outlines the core structures of different beta-lactam antibiotics. All these structures share a common chemical moiety, known as a beta-lactam ring (highlighted in red). The beta-lactam ring is mainly responsible for the antibacterial properties of these molecules [2]. Beta-lactam antibiotics inhibit the growth of sensitive bacteria by inactivating enzymes located in the bacterial cell membrane, known as penicillin-binding proteins, which are involved in cell wall synthesis [3].

Figure 1: Core structures of different classes of beta-lactam antibiotics

Source: De Rosa M, Verdino A, Soriente A, et al. 2021. The Odd Couple(s): An Overview of Beta-Lactam Antibiotics Bearing More Than One Pharmacophoric Group. *International Journal of Molecular Sciences* 22(2): 617. URL: https://www.mdpi.com/1422-0067/22/2/617(accessed 14 November 2022).

2.1.1 Classification and indications of cephalosporins

Cephalosporins are grouped into five generations based on their antibacterial properties and their discovery [4].

Table 1 shows the different generations of approved (and available) cephalosporins in NZ, their indications, PHARMAC funding, route of administration and dosing interval.

Most cephalosporins approved in NZ are indicated for children and adults. Cefepime is approved in children over 12 years of age, and ceftolozane/tazobactam is only indicated for adults [5].

Antibiotic choice, dosing and route of administration is influenced by several factors. This includes history of an allergy, renal and hepatic function, severity of illness, location of infection, and antimicrobial susceptibility [6]. Cephalosporins may be used as an alternative first line treatment to penicillin antibiotics in individuals who have a history of a penicillin reaction that is not life-threatening [6].

Local antibiotic guidelines provide empiric recommendations for treatment of different infections, often based of local susceptibility information. Once microbiology sensitivities are known, therapy may be changed to a

narrow spectrum agent [6, 7]. For serious and complicated infections, advice on appropriate antibiotic choice and dosing is often sought from infectious disease specialists [7].

Table 1: Approved and available cephalosporins in New Zealand: generation, indication, funding, route of administration and dosing interval

Cephalosporin: Product name (sponsor and date of data sheet)	Indication as per NZ data sheet	PHARMAC funding	Route of administration	Dosing interval range
1st generation				
Cefazolin Cefazolin-AFT (AFT Pharmaceuticals, 2 Aug 2022)	Respiratory tract infections, genitourinary tract infections, biliary tract infections, septicaemia, endocarditis, perioperative prophylaxis, bone and joint infections	Community[a] Hospital	IM/IV	6–12 hourly
Cefalexin Cefalexin (Flynn Granules) (Max Health, 19 Nov 2021) Cefalexin Sandoz (Novartis, 9 Dec 2016) Cephalexin ABM (Boucher & Muir NZ Ltd t/a BNM group, 4 Mar 2019)	Bacterial sinusitis, respiratory tract infections, skin and skin-structure infections, bone infections, genitourinary tract infections, dental infections, otitis media	Community Hospital	PO	6–12 hourly
2nd generation				
Cefuroxime Cefuroxime-AFT (AFT Pharmaceuticals Ltd, 9 Jan 2020) Zinacef (GSK NZ Ltd, 16 Nov 2020)	Respiratory tract infection, ear, nose and throat infections, urinary tract infections, soft tissue infection, bone and joint infections, gonorrhoea, septicaemia, meningitis, peritonitis, perioperative prophylaxis, obstetric and gynaecological infections	Hospital	IV	6–12 hourly
Cefuroxime axetil Zinnat (GSK NZ Ltd, 24 Nov 2021)	Respiratory tract infection, genitourinary infections, skin and soft tissue infections, gonorrhoea, acute uncomplicated gonococcal urethritis, cervicitis	Community[b] Hospital	PO	12–24 hourly
Cefaclor Ranbaxy-Cefaclor (Douglas Pharmaceuticals Ltd, 28 Dec 2018)	Respiratory tract infections, otitis media, skin and soft tissue infections, urinary tract infections, skin and skin structure infections, sinusitis, gonococcal urethritis	Community Hospital	PO	8–12 hourly
3rd generation				
Cefotaxime DBL Cefotaxime Sodium (Pfizer NZ Ltd, 15 Oct 2020)	Septicaemia, respiratory tract infection, urinary tract infections, soft tissue infections, bone and joint infections, obstetric and gynaecological infections, meningitis, perioperative prophylaxis	Hospital	IM/IV	6–24 hourly
Ceftazidime Ceftazidime Kabi (Fresenius Kabi, 24 Sep 2021) Ceftazidime-AFT (AFT Pharmaceuticals Ltd, 27 Jun 2019) Zavicefta (ceftazidime + avibactam) (Pfizer, 4 Oct 2022)	Severe infections including septicaemia, bacteraemia, peritonitis, meningitis, infections in immunosuppressed patient, infections in intensive care, respiratory tract infections (including in cystic fibrosis), ear, nose and throat infections, urinary tract infections, skin and soft tissue infections, gastrointestinal, biliary, abdominal infection, bone and joint infections, infections associated with haemo- and peritoneal dialysis, and with continuous ambulatory peritoneal dialysis	Hospital[c]	IV/IM	8–12 hourly
Ceftriaxone Ceftriaxone (Devatis, Aug 2021) Ceftriaxone-AFT (AFT Pharmaceuticals Ltd, 28 Jul 2020)	Sepsis, meningitis, abdominal infections, infections of the bones, joints, soft tissue, skin, wound infection, renal and urinary tract infections, genital infections, perioperative prophylaxis, infection in patients with impaired defence mechanisms	Community[d] Hospital	IV/IM	24-hourly
4th generation				

Cephalosporin: Product name (sponsor and date of data sheet)	Indication as per NZ data sheet	PHARMAC funding	Route of administration	Dosing interval range
Cefepime Cefepime Kabi (Fresenius Kabi New Zealand, 15 Jan 2020) Cefepime-AFT (AFT Pharmaceuticals Ltd, 18 Jan 2018)	Lower respiratory infections, urinary tract infections, skin and skin structure infections, intra-abdominal infections, septicaemia, empiric treatment in febrile neutropenic patients	Hospital[e]	IV/IM	8 – 12 hourly
5th generation				
Ceftaroline fosamil Zinforo (Pfizer NZ Ltd, 5 January 2021)	Complicated skin and soft tissue infections, community-acquired pneumonia	Hospital[f]	IV	8 – 12 hourly
Ceftolozane Zerbaxa (ceftolozane + tazobactam) (Merck Sharp & Dohme NZ Ltd, 26 Feb 2021)	Complicated intra–abdominal infections in combination with metronidazole, complicated urinary tract infections, including pyelonephritis, nosocomial pneumonia	Not funded	IV	8 hourly

Key: IM = intramuscular; IV = intravenous; PO = oral

Notes:

a. Only for dialysis or cellulitis in accordance with a Health NZ hospital approved protocol.
b. Only if prescribed for prophylaxis of endocarditis.
c. Only when prescribed or recommended by a clinical microbiologist, infectious diseases specialist, or respiratory specialist, or in accordance with a protocol or guideline that has been endorsed by the Health NZ hospital.
d. Only if prescribed for dialysis or cystic fibrosis patient, or the treatment of gonorrhoea, or the treatment of pelvic inflammatory disease, or the treatment of suspected meningococcal disease.
e. Prescribed by or recommended by a clinical microbiologist or infectious disease specialist, or in accordance with a protocol or guideline that has been endorsed by the Health NZ hospital.
f. Multi-resistant organism salvage therapy, prescribed by, or recommended by a clinical microbiologist or infectious disease specialist, or in accordance with a protocol or guideline that has been endorsed by the Health NZ hospital, and for patients where alternative therapies have failed or who have a contraindication or hypersensitivity to standard current therapies.

Sources:

- Indications, route and dosing interval from the product data sheets, published at: https://www.medsafe.govt.nz/Medicines/infoSearch.asp
- Funding: PHARMAC Community Schedule, URL: https://schedule.pharmac.govt.nz/ScheduleOnline.php; PHARMAC Hospital Medicines List (HML), URL: https://schedule.pharmac.govt.nz/HMLOnline.php

First generation cephalosporins

First generation cephalosporins have coverage against most gram-positive cocci such as staphylococci species and streptococci species, while having minimal coverage against gram-negative bacteria [4]. Cefazolin is a first-generation cephalosporin. It is administered parenterally and is often used for skin and soft tissue infections, and for perioperative prophylaxis [4, 6]

Cefalexin and cefaclor are orally-administered cephalosporins and have a similar antimicrobial spectrum. They are used for infections managed in primary care, including urinary tract infections, respiratory tract infections, otitis media and skin and soft tissue infections managed in primary care [6]. They may also be used when a patient is being discharged from hospital and needs to be switched from intravenous to oral cephalosporins to complete the antibiotic course [7].

Second generation cephalosporins

Second generation cephalosporins have less activity against gram-positive cocci than first generation cephalosporins, but have increased activity against gram-negative bacteria [4]. When given intravenously in combination with metronidazole, cefuroxime is used as an alternative option to amoxicillin-based regimens for treatment of gastrointestinal infections, such as peritonitis, diverticulitis or intra-abdominal abscesses. It is also used as monotherapy (or in combination) for pyelonephritis [7].

Cefoxitin is a second-generation cephalosporin [4]. There is currently an approved product, however it is not being marketed in NZ and there is no published data sheet on the Medsafe website.

Third generation cephalosporins

Third generation cephalosporins have extended gram-negative coverage. Compared to previous generations of cephalosporins, these antibiotics are more likely to be used for serious infections and infections in immunocompromised individuals [4]. Immunocompromised individuals are at risk of acquiring antimicrobial resistant infections, and therefore require a broad spectrum of microbial cover [6, 7].

Third generation cephalosporins are used in the treatment of bacterial meningitis. Ceftriaxone is often used first line as an empiric (based on experience of the infection before the pathogen is known) antibiotic for bacterial meningitis, and may be given in the community before the patient is transferred to hospital [8]. Ceftazidime has pseudomonas coverage and is used in patients who have had a previous pseudomonas infection or previous colonisation [6].

Fourth generation cephalosporins

Fourth generation cephalosporins have similar coverage to third generation cephalosporins, with additional coverage against gram-negative bacteria that have antimicrobial resistance. Cefepime is a fourth-generation cephalosporin and may be reserved for serious systemic infection in patients who are likely to have multi-resistant organisms [4].

Fifth generation cephalosporins

Fifth generation cephalosporins, such as ceftaroline and ceftolozane, have coverage against methicillin-resistant staphylococci and penicillin-resistant pneumococci [4]. Ceftaroline is only funded for multi-resistant organism salvage therapy where alternative therapies have failed [9].

Comments

There are a range of cephalosporins approved in NZ.

Cefalexin and cefaclor are oral antibiotics and commonly used in primary care for mild to moderate infections. Other cephalosporins are administered parenterally and are used in hospital with a few exceptions.

Third, fourth and fifth generation cephalosporins have a broad antimicrobial spectrum and are used for serious infections.

Use of cephalosporins in secondary care is guided by local treatment guidelines. Infectious disease clinician approval may be required before third, fourth and fifth generation cephalosporins are used.

2.1.2 Usage

Information on the number of people dispensed an approved and community-funded cephalosporin is outlined in Table 2.

Cefuroxime (IV), cefotaxime, ceftazidime, cefepime, ceftaroline and ceftolozane are unlikely to be used in the community. Therefore, usage data for these cephalosporins is unavailable.

Table 2: Number of people dispensed an approved and community-funded cephalosporin in 2018–2020

Cephalosporin	Number of people dispensed*			
	2018	2019	2020	2021
Cefazolin	1558	1368	1207	959
Cefalexin	150,687	168,217	156,165	186,451
Cefuroxime (oral)	329	355	351	342
Cefaclor	81,197	68,771	52,240	42,297
Ceftriaxone	299	318	356	363
Ceftazidime	n/a	n/a	n/a	n/a

* Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year.

Source: Ministry of Health 2022. Pharmaceutical Data web tool version 7 November 2022 (data extracted from the Pharmaceutical Collection on 10 August 2022) URL: https://minhealthnz.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 14 November 2022).

Comments:

Cefalexin is the most used cephalosporin in the community, followed by cefaclor. Both are the only orally-administered cephalosporins available in NZ.

Cefazolin and ceftriaxone use in the community is low.

Usage data is not available for most cephalosporins, as they are administered in or supplied from a hospital.

Long-term antibiotic use may be indicated for the management of certain infections, whereby a patient is administered the antibiotic parenterally by a continuous infuser or by injection via district nurse. This allows continuation of parental antibiotic therapy in the community after discharge from hospital.

2.2 Cephalosporins and neurotoxicity

2.2.1 Signs and symptoms

Clinical presentation of cephalosporin-induced neurotoxicity (CIN) includes a range of symptoms that may vary between individuals. Cases associated with CIN are characterised by encephalopathy, myoclonus and/or seizures [10, 11].

Encephalopathy is a broad term for any diffuse disease of the brain that alters brain function or structure, regardless of aetiology and pathophysiology. It does not refer to a single disease, but rather to a syndrome of overall brain dysfunction [12].

CIN has been reported to cause an acute toxic/metabolic encephalopathy (TME) [13]. The most defining clinical feature of encephalopathy is an altered mental state, which may be represented as delirium, confusion and/or depressed level of consciousness. Other symptoms may include agitation, hallucinations and

disorientation. A variety of motor abnormalities may also be observed in acute TME, such as tremor and myoclonus [14].

Seizures have also been reported in cases of CIN, and may be a manifestation of acute TME [14]. A seizure is a burst of uncontrolled electrical activity between neurons that causes temporary abnormalities in muscle tone, behaviours, sensations or states of awareness. A seizure may also be called a 'convulsion', which relates to the involuntary contraction of muscles which occur during most seizure types [15]. Non-convulsive status-epileptics (NCSE) has also been reported with CIN. NCSE refers to a prolonged seizure that manifests as an altered mental state as opposed to convulsions. Electroencephalogram (EEG) monitoring is required to detect NCSE [16].

Other symptoms reported with CIN include myoclonus (muscle jerks), agitation, and hallucinations [10].

The typical time period for CIN is between 2 to 10 days following the initiation of cephalosporin treatment [17]. Mental status changes may appear initially. Continued administration may lead to myoclonus and seizures [18].

Comments:

Symptoms of CIN may include encephalopathy (identified by symptoms relating to changes in mental state), myoclonus and seizures (including NCSE).

2.2.2 Proposed mechanism

Normal neuronal activity requires a balanced environment for optimal central nervous system (CNS) function [19].

The pathophysiology of acute TME varies according to the underlying cause. All forms interfere with the function of the ascending reticular system and/or its projections into the cerebral cortex, leading to impairment of arousal and/or awareness. Direct CNS toxicity by cephalosporins may result in a drug-induced encephalopathy [14].

Cephalosporin-induced seizures are thought to result from disruption in the neurotransmitter gamma-aminobutyric acid (GABA) function [20]. The structure of GABA is shown in Figure 2 [19]. GABA is an inhibitory neurotransmitter in the brain. It serves to maintain inhibitory tone that counterbalances neuronal excitation. GABA blocks neuronal communication by binding to $GABA_A$ receptor ($GABA_AR$), present on the postsynaptic membrane. Binding of GABA to the receptor leads to influx of chloride ions, membrane hyperpolarization, and reduced firing of neurons. GABA antagonists may produce neuronal excitability and convulsions by binding to the $GABA_AR$, blocking the GABA binding sites [20].

Figure 2: Structure of gamma-aminobutyric acid (GABA)

Source: Treiman DM. 2001. GABAergic mechanisms in epilepsy. *Epilepsia* 42 Suppl 3: 8-12. DOI: 10.1046/j.1528-1157.2001.042suppl.3008.x (accessed 26 October 2022).

Cephalosporins are competitive antagonists of the $GABA_AR$ and inhibit the action of GABA [20]. The beta-lactam ring shares similar structural characteristics to GABA, facilitating receptor inhibition. Through dose-dependent GABA inhibition, an increase in excitatory neurotransmitter activity may occur [21]. This mechanism appears to be associated with the capacity of cephalosporins to induce convulsions [17]. Structural differences between cephalosporins may influence their binding at the receptor and potential convulsive effects [20].

Sugimoto et al (2003) examined the convulsive activities of several cephalosporins by intracerebroventricular administration in mice. Receptor binding affinity of $GABA_A$ receptor and N-methyl-d-aspartate (NMDA) receptor were also assessed. Cefazolin had more potent convulsive activity than cefepime and ceftazidime. The results from the study suggested that beta-lactam antibiotics exert convulsive activity at higher concentrations, bind to $GABA_A$ receptors in a concentration-dependent and competitive manner, and NMDA receptors are not involved in convulsive activity. While suggestive, these results do not quantify completely clarify the convulsive risk of cephalosporins in a clinical situation [22].

Comments:

Encephalopathy may arise from cephalosporin exposure in the CNS that affects the normal neuronal functioning in the brain.

Cephalosporins may inhibit $GABA_A$ binding, which could be a biologically plausible mechanism for convulsive effects.

The potential convulsive effects of cephalosporins may vary due to their different structures.

2.2.3 Risk factors

Risk factors for cephalosporin-induced neurotoxicity include renal impairment, blood brain barrier (BBB) penetration, BBB disruption and plasma and cerebrospinal fluid (CSF) levels. These risk factors are discussed below.

2.2.3.1 Renal impairment

Renal impairment has been recognised as a significant contributing factor to CIN, especially if the cephalosporin dose is not appropriately renally-adjusted [23].

Renal function can be measured via estimated glomerular filtration rate (eGFR) or creatinine clearance. eGFR is normalised to a body surface area of $1.73m^2$. Creatinine clearance (CrCl) is calculated using Cockcroft and Gault equation using the patient's age, gender and weight [24].

In renal failure, the kidneys are not able to function properly and eGFR/CrCl is lower than normal. Established renal failure is when the eGFR is less than 15 mL/minute/1.73^2. A reduction in kidney function may progress over time (chronic kidney disease) or be sudden in onset (acute kidney injury) [24].

Table 3 outlines the elimination pharmacokinetic (PK) parameters of different cephalosporins.

Table 3: Elimination pharmacokinetic parameters of different cephalosporins in adults

Cephalosporin	Renal excretion	T ½ (normal renal function)	T ½ (renal failure)
Cefazolin	70-80%[a]	1.8 hours[a]	11–13 hours[b]
Cefalexin	>90%[a]	0.5-1.2 hours[a]	16 hours[c]
Cefuroxime	66- 100%[a]	1-2 hours[a]	17 hours[c]
Cefaclor	60–85%[a]	0.6-0.9 hours[a]	2.3–2.8 hours[c]
Cefotaxime	approximately 60%[a]	1–1.5 hours[a]	2.5 hours (10 hours for the metabolite)[c]
Ceftazidime	80–90%[a]	1-2 hours[a]	13–25 hours[c]
Ceftriaxone	33–67%[a]	5–9 hours[a]	12-16 hours[a]
Cefepime	85%[a]	2 hours[a]	13–19 hours[b]
Ceftaroline fosamil	88%[a]	2.5 hours[c]	n/a (increased)[c]
Ceftolozane	>95%[a]	3–4 hours[a]	n/a

Key: T ½= Half-life. The time required for half for the medicine to be removed from the body.

Notes:

a. Source: UpToDate, Product monograph - Pharmacokinetics. URL: https://www.uptodate.com/contents/search (accessed 31 October 2022).
b. Source: Micromedex, Product monograph – Pharmacokinetics. URL: https://www.micromedexsolutions.com (accessed 31 October 2022).
c. Source: The Renal Drug Handbook (5th edition, 2019), UK Renal Pharmacy Group, Product monograph. URL: https://www.medicinainterna.net.pe/sites/default/files/The_Renal_Drug_Handbook_The_Ultimate.pdf (accessed 31 October 2022)

As shown in Table 3, cephalosporins are eliminated from the body mostly by the kidneys. Clearance of cephalosporins by the kidneys is decreased in renal impairment, shown by an increase in the half-life (T ½). When cephalosporin doses are not reduced in renal impairment, accumulation can occur, potentially leading to toxic effects [24].

Ceftriaxone is different to other cephalosporins in that it undergoes both renal and bile excretion. It also has a long half-life in people with normal renal function, compared with other cephalosporins [25].

Comments

Cephalosporins are renally cleared and therefore require dose reductions in renal impairment.

Dose reductions for cefazolin, ceftazidime, cefepime, ceftaroline and ceftolozane/tazobactam are required both in moderate and severe renal impairment (<50 mL/min). Whereas the CrCl threshold for dose reduction for other cephalosporins is around 10–20 mL/min.

Patients who are seriously unwell are likely to have fluctuating renal function, making it challenging for calculation of renal function and ensuring appropriate dosing. Regular monitoring of renal function throughout treatment is important.

Care should also be taken when using other medicines that may acutely impact renal function.

Calculation of creatinine clearance via the Cockcroft and Gault equation may be a more accurate representation of renal function in patients with extremes of weight. eGFR is likely an overestimation of renal function in a frail older adult and may lead to overdosing. Hepatic impairment may increase the risk of accumulation of ceftriaxone.

2.2.3.2 Blood-brain barrier (BBB) penetration

The BBB is a dynamic structure that protects the brain against harmful blood-borne pathogens and toxins, and maintains the homeostatic environment [26]. It is formed by a monolayer of endothelial cells fused together to form intercellular tight junctions. These cells help to control the entry and exit into the CNS [27]. Figure 3 highlights the different mechanisms used by molecules to cross the BBB [28]. Molecules may enter through the tight junctions (paracellular) or through the cell wall via transport systems (transcellular) [27, 28].

Figure 3: Diagram of endothelial cells that form the blood-brain barrier and pathways across the blood-brain barrier

Source: Alahmari A. 2021. Blood-Brain Barrier Overview: Structural and Functional Correlation. *Neural plasticity* 2021: 6564585-6564585. DOI: 10.1155/2021/6564585 (accessed 14 November 2022).

Cephalosporins enter the CSF predominantly via passive diffusion down a concentration gradient. Due to their low lipophilicity, they transverse cell membranes poorly and enter the CSF slowly via paracellular pathways [29]. The concentration time-curve of cephalosporins in the CSF lags behind plasma [30].

The extent of penetration of different cephalosporins through the intact BBB is variable, due to differences in lipophilicity, protein binding and plasma concentration. Patient factors such as renal function and albumin levels also influence the pharmacokinetics of these medicines [29]. Cephalosporins exhibiting a moderate lipophilicity were found to diffuse well into the CSF [31]. The PK parameters of third and fourth generation cephalosporins are similar, with the exception of ceftriaxone [29].

Binding to plasma proteins influences the entry of a drug into the CNS. Only the plasma fraction of unbound (free) drug can penetrate an intact BBB, as binding proteins (eg, albumin and globulins) pass through the BBB only to a small degree [31]. Table 4 shows the protein binding of different cephalosporins.

Some conditions, such as renal disease or low albumin, reduce the amount of proteins available for binding. For highly protein-bound drugs, a reduction in binding proteins results in an increase of unbound drug in the

plasma – meaning more is available to cross the BBB [30]. Cefazolin and ceftriaxone are highly protein-bound cephalosporins.

Table 4: Protein binding (%) of different cephalosporins

Cephalosporin	Protein binding (adults)
Cefazolin	80%
Cefalexin	10–15%
Cefuroxime	33–50%
Cefaclor	25%
Cefotaxime	31–50%
Ceftazidime	<10%
Ceftriaxone	85–95%
Cefepime	20%
Ceftaroline	20%
Ceftolozane	16–21%

Source: UpToDate Product Monographs – Pharmacokinetics URL: https://www.uptodate.com/contents/search (accessed 1 November 2022).

Treatment of CNS infections relies on BBB penetration of antibiotics to reach effective levels in both un-inflamed and inflamed meninges [31]. The third generation cephalosporins (ceftriaxone, ceftazidime and cefotaxime) are approved for treatment of meningitis. Cefalexin and cefaclor achieve relatively low CSF concentrations and are not currently used for treatment of meningitis. Ceftaroline and ceftolozane are newer cephalosporins and appear to cross the BBB, however more research is needed for their use in CNS infections [29].

Comments

The extent of penetration across the intact BBB varies between different cephalosporins, and likely impacts their concentration in the CNS.

Elevation of cephalosporins plasma levels, due to reduced clearance in renal impairment and/or reduced protein binding, may influence CSF concentrations due to passive diffusion and concentration gradients.

2.2.3.3 Blood brain barrier disruption

A disturbed BBB may lead to the enhanced transfer and accumulation of cephalosporins in the brain or cerebrospinal fluid (CSF), interfering with neuronal function [14, 20].

Factors that influence BBB permeability include chemical mediators (such as bradykinin, substance P, histamine, thrombin, endothelin-1) and inflammatory cytokines (such as IL-1 and TNF-a). These may be associated with inflammation-related mechanisms, and alter the expression of tight junctions and the function of transporters on the BBB [26].

Patients with severe illness, such as those treated in ICU and/or patients with sepsis, are also prone to disruptions in BBB integrity due to meningeal inflammation [12].

Comments:

BBB disruption increases the permeation of cephalosporins into the CNS.

Under conditions where the BBB is disrupted, the physiochemical properties of medicines that govern entry to the CNS is less important.

Critically ill patients are prone to disruptions in BBB.

2.2.3.4 Plasma and CSF levels

When reported, some case reports correlate an increase in serum plasma levels and/or CSF levels of cephalosporin with CIN [23, 32].

Measuring the concentration of cephalosporins in the plasma and CSF may give an idea of cephalosporin exposure. However, the relationship between the level of exposure to a cephalosporin and the onset of neurotoxicity has not been established [23].

Plasma concentration alone is likely unable to estimate CSF concentration because of different CSF/plasma ratios and BBB efflux among patients [30].

Comments:

There is insufficient available information to define the plasma and CSF level associated with cephalosporin neurotoxicity. It is unclear what plasma levels should be targeted or what CSF levels could be toxic or whether measuring these would help reduce the risk of neurotoxicity.

In some cases of CIN, the patients had renal dysfunction and were not dosed appropriately for their condition. This inappropriate dosing could be considered an overdose. If the patients had been dosed appropriately, neurotoxicity may not have occurred.

Seizures and encephalopathy are reported as symptoms of overdose in several cephalosporin data sheets, suggesting that when used at more than the recommended dosages, neurotoxicity may occur.

Cephalosporins do not generally require therapeutic drug monitoring compared with some other antibiotics such as vancomycin or gentamycin. The ceftazidime data sheet states that trough levels should not exceed 40mg/mL when treating severe infections. The ceftriaxone data sheet recommends monitoring plasma concentration in patients undergoing dialysis. The Australian PI includes that blood levels should be monitored in patients with severe renal impairment and that serum levels should not exceed 280 micrograms/mL. There is no information about the risk of adverse effects in relation to the monitoring recommendations.

2.2.3.5 Summary

Many risk factors have been identified for CIN, however, most have been identified via case reports.

High plasma concentrations of cephalosporins resulting from reduced clearance and/or excessive dosing, in conjunction with an increased permeability of the BBB (such as in severe infections), may increase CNS levels and contribute to neurotoxicity. Individuals with underlying CNS disease or who are elderly may be more susceptible to CIN.

A combination of these factors may cause an increase in the levels of cephalosporins in the CNS, and in conjunction with the patient's susceptibility, the potential for neurotoxicity.

2.2.4 Differential diagnosis

Neurotoxic symptoms with similar clinical features to CIN are common in critically ill patients. Distinguishing CIN among these patients is challenging [18].

There are many other types of acute TME, including septic, electrolyte disturbance, hepatic (advanced cirrhosis of the liver) and uremic (high levels of toxics normally cleared by the kidney). Acute TME can also occur from other medicines, illicit drugs, and alcohol. Clinical features of acute TME are nonspecific, and do not reliably identify the underlying cause [14].

Infectious diseases may affect brain function and cause encephalopathy even when the pathogen does not directly infect the CNS. Infections caused by viruses, bacteria or parasites may lead to a secondary

inflammatory response in the brain, also known as neuroinflammation, mediated by cytokines and chemokines. Neuroinflammation has been linked to cognitive and behavioural symptoms [12].

Delirium is common in a hospitalised patient. Other risk factors for delirium include older age, baseline cognitive impairment, mechanical ventilation and the post-operative setting [11].

Electrolyte disturbances, medicines, withdrawal effects, sepsis, fever and CNS infections (such as meningitis and encephalitis) may also cause a provoked seizure [20].

NCSE can occur in the ICU and is more common that previously recognised. Any fluctuating or unexplained alternation in behaviour or mental status warrants consideration of NCSE and evaluation of EEG [16].

Comments:

Individuals may be at risk of encephalopathies and/or seizures caused by infection, liver and kidney impairment and other medicines.

The presence of these factors in patients who are receiving cephalosporin therapy may complicate the recognition of CIN.

2.2.5 Diagnosis and management

Diagnosis of CIN is mainly by clinical suspicion, however, may include diagnostic imaging. It is recommended that EEG studies are performed in patients who present with neurological complications during the course of treatment with cephalosporins [20].

Different EEG patterns have been described in association with CIN. Both encephalopathy with triphasic waves and NCSE have been reported, and distinguishing between these two conditions may be difficult [33].

Early detection of drug-induced seizures is important. Cessation of the antibiotic is critical in preventing seizure recurrence. Drug-induced seizures are typically self-limiting, however repetitive prolonged seizures may require medical management [20].

Management of CIN includes cessation of cephalosporin use, initiation of anticonvulsive therapy if indicated, and intermittent haemodialysis in those with compromised renal function [34]. Symptoms of CIN are usually resolved following discontinuation of the cephalosporin [10].

Comments

EEG monitoring is helpful in patients taking cephalosporins who present with an altered mental state and no other obvious causes for the presentation.

Discontinuation of the cephalosporin in CIN usually resolves symptoms. However, in patients with renal impairment, the half-life will be extended and dialysis may be required for rapid removal of the medicine.

3 SCIENTIFIC INFORMATION

3.1 New Zealand and international prescribing information

The NZ data sheets for approved and available cephalosporins were reviewed against Australian and UK product information for neurological adverse events.

The product information used in this section was sourced from the following websites:

- New Zealand data sheets: Medsafe Information for Prescribers/Consumers Search (medsafe.govt.nz)
- Australian product information (PI): Therapeutic Goods Administration TGA eBusiness Services
- UK summary of product characteristics (SmPC): About emc - electronic medicines compendium (emc)

3.1.1 Neurological adverse effects

A summary of the neurological adverse effects listed in New Zealand, Australian and UK product information is presented below.

For further information, refer to annex 1.

3.1.1.1 First generation cephalosporins

The Australian and UK cefazolin product information includes a warning in section 4.4 that seizures may occur in patients with renal impairment/inappropriately high doses administered in renal impairment.

The Australian PI includes an additional warning for encephalopathy with use of cefazolin in renal failure.

Confusion, hyperactivity, and drowsiness are listed in section 4.8 of the UK SmPC.

Seizures is included in section 4.9 (overdose) of the NZ, Australian and UK product information.

The cefalexin product information in NZ, Australia and UK has no warnings about encephalopathy and/or seizures. A general statement about overdosage of cephalosporins is included in the NZ and Australian product information.

3.1.1.2 Second generation cephalosporins

Reversible hyperactivity, confusions, hypertonia, and hallucinations are listed in section 4.8 of cefaclor data sheet. These symptoms could represent encephalopathy.

Section 4.8 of the cefaclor NZ data sheet has a general statement about cephalosporins triggering seizures, particularly in patients with renal impairment. If seizures associated with medicine therapy occur, the medicine should be discontinued, and anticonvulsant therapy can be given if clinically indicated.

There is no information about seizures in section 4.9 of cefaclor data sheet, Australian PI or UK SmPC. product information.

Section 4.9 of the cefuroxime IV Australian PI and UK SmPC state that encephalopathy and coma, in addition to convulsion, are symptoms of overdose. The cefuroxime NZ data sheet lists convulsions only in section 4.9. No information is listed in section section 4.4 or 4.8 of the NZ data sheet, Australian PI or UK SmPC.

3.1.1.3 Third generation cephalosporins

The cefotaxime NZ, Australian and UK product information contains warnings about neurotoxicity. This warning notes that cefotaxime, especially in patients with kidney failure, may lead to encephalopathies (e.g., loss of consciousness, abnormal movements, and convulsions). Risk of encephalopathy is also listed in section 4.7.

Section 4.9 of the UK cefotaxime SmPC states that the risk of encephalopathies and CNS excitation conditions is increased in patients with severely restricted kidney function, epilepsy, and meningitis. The NZ data sheet does not include the additional information about risk factors.

Sections 4.4 and 4.8 of the ceftazidime product information include that there have been reports of neurological sequelae (including tremor, myoclonia, convulsions and encephalopathy) in patients with renal impairment whom the dose has not been appropriately reduced.

The NZ ceftriaxone data sheet does not include information about neurological adverse effects. Encephalopathy is included in the Australian and UK product information.

3.1.1.4 Fourth generation cephalosporins

The cefepime product information includes warnings relating to encephalopathy, myoclonus, and seizures. Most reports have occurred in patients with renal impairment who received doses of cefepime that exceeded recommendations.

Section 4.4 states that, in general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after haemodialysis. However, some cases included a fatal outcome, which is included in the NZ data sheet and Australian PI.

3.1.1.5 Fifth generation cephalosporins

The ceftaroline product information includes information about neurological sequalae, including encephalopathy occurring when appropriate dose adjustments are not made. In addition, ceftaroline should be used with caution in patients with a history of seizures, due to seizures occurring in toxicology studies.

Section 4.9 of the UK ceftaroline SmPC includes information about neurotoxic effects, which is not in section 4.9 of the NZ and Australian product information.

The NZ, Australian and UK prescribing information for ceftolozane + tazobactam has no information about neurotoxicity.

3.1.1.6 Summary of neurological adverse effects in product information

Table 5 provides a summary of the information relating to neurotoxic adverse effects currently in NZ data sheets.

Table 5: Summary of cephalosporin—induced neurotoxicity in New Zealand cephalosporin data sheets, by symptom and data sheet location

	Encephalopathy	Seizures/convulsions	Myoclonus	Other
Cefazolin	-	4.9	-	-
Cefalexin	-	4.9	-	4.8: Confusion, headache, agitation, hallucinations. 4.9: hallucinations, hyperreflexia
Cefuroxime IV + PO	-	4.9	-	-
Cefaclor	-	4.8	-	4.8: Reversible hyperactivity, confusion, hallucinations. somnolence
Cefotaxime	4.4, 4.7, 4.8, 4.9	4.4, 4.8		4.8/4.4: confusion, headache, agitation, loss of consciousness, abnormal movements. 4.7
Ceftazidime	4.8, 4.9	4.8, 4.9	4.8, 4.9	4.4: Neurological sequelae 4.8/4.9: coma, tremor
Ceftriaxone	-	-	-	-
Cefepime	4.2, 4.4, 4.8, 4.9	4.2, 4.4, 4.8. 4.9	4.2, 4.4, 4.8, 4.9	4.2/4.4/4.8/4.9: disturbance of consciousness, confusion, hallucination, stupor, coma, neuromuscular excitability.
Ceftaroline	4.4, 4.8	4.4	-	4.4/4.8: neurological sequalae.
Ceftolozone	-	-	-	-

There is variable information relating to CIN in the NZ data sheets. Cefepime-induced neurotoxicity is well-documented throughout the data sheet. Ceftazidime, cefotaxime and ceftaroline have a warning in section 4.4. Ceftriaxone has no information.

There is a range of different symptoms reported across the data sheets. Some data sheets include encephalopathy, and list symptoms such as confusion, myoclonus and seizures. Others include encephalopathy (with list of symptoms of mental state changes), and also list myoclonus and seizures as separate ADRs. Some data sheets only include seizures.

Both cefalexin and cefaclor, which are oral cephalosporins, list confusion, hallucinations, and hyperreflexia/hyperactivity in the data sheets. These are potential symptoms of encephalopathy.

Where information on encephalopathy and seizures is listed, most data sheets note renal dysfunction and/or when the dosage reduced in renal function as risk factors for neurotoxicity.

3.1.2 Renal dose adjustments

A summary of renal dose adjustments of cephalosporins for adults in the NZ datasheets, versus international prescribing information and other prescribing resources, is presented in the section below.

For further information refer to annex 2.

3.1.2.1 First generation cephalosporins

The recommended dosing orf cefazolin in the NZ data sheet varies depending on the indication. Higher doses are used in severe, life-threatening infections.

Dose reduction of cefazolin is required when CrCl is <55 mL/min. Renal dose adjustments in the cefazolin NZ data sheet are the same as in the UK SmPC. Dose adjustments apply after an initial loading dose appropriate to the infection. Dose adjustments are calculated by halving the full dose required and/or extending the frequency. The data sheet does not provide information on dosing in dialysis.

Compared to the NZ data sheet and UK SmPC, the recommended cefazolin doses for severe renal impairment are lower in the Australian product information and UpToDate. For serious infections, the NZ data sheet recommends 1–1.5g every 6 hours. This is reduced to 500–750mg every 18–24 hours if CrCl <10 mL/min. Using the Australian information, for a severe infection, the dose would be reduced to 150–400mg every 24 hours when CrCl between 5–20 mL/min, and 75-200mg every 24 hours when CrCl <5 mL/min. The recommended dose in UpToDate for ≤10 mL/minute: 500 mg to 1 g every 24 hours.
The maximum dose of cefazolin in the Australian and UK information is up to 6g a day. The NZ data sheet states that doses up to 12g have been used rarely.

Comments:

Cefazolin is funded in the community for dialysis. The NZ cefazolin data sheet has no dosing information for use in dialysis.

Dosing in severe renal impairment differs between the NZ and Australian product information.

The usual dose of cefalexin ranges from 1 to 4 grams. Section 4.4 of the NZ, Australian and UK product information advises that cefalexin should be administered with caution in patients with markedly impaired renal function, and that a safe dosage may be lower than that usually recommended.

Prescribing guidelines, including the NZF, suggest a lower dose should be used in renal impairment and provide dosing recommendations.

Comments:

The cefalexin NZ data sheet recommends caution with use in renal impairment; however, no dose adjustments are provided.

3.1.2.2 Second generation cephalosporins

The cefuroxime dose should be renally adjusted when it is given intravenously to patients with CrCl <20mL/min. Dose adjustment recommendations in the cefuroxime (IV) NZ data sheet are the same as the UK SmPC and include dialysis.

The cefuroxime IV Australian PI has a maximum dose of 1.5g every 24 hours in patients with CrCl <20 mL/min. UpToDate and the Renal Drug Handbook guidance also have this this maximum dose. The NZ data sheet and the UK SmPC recommend 750mg once daily for CrCl <10 mL/min.

The dose of cefuroxime axetil, administered orally, should be reduced when CrCl is <30 mL/min.

Renal dose adjustments of cefaclor are generally not required. Cefaclor has a short half-life.

Comments:

The maximum dose of cefuroxime (IV) in patients with severe renal impairment is lower in the NZ data sheet and UK SmPC, compared to Australian product information and other prescribing information.

Cefaclor does not require renal dose adjustment, however product information states that it should be used with caution in the presence of markedly impaired renal function.

3.1.2.3 Third generation cephalosporins

Dosing recommendations for ceftazidime are the same in the NZ, Australian and UK product information. Dosing guidance for ceftazidime for different types of dialysis are also in the NZ data sheet. It is recommended a lower maximum dose (3g) of ceftazidime is used in elderly, especially over 80 years of age.

There is variation between renal dosing recommendations of cefotaxime across international prescribing information and prescribing guidelines. The NZ data sheet recommends dose reduction when CrCl is <10 mL/min. The Australian and UK product information suggest dose reductions when CrCl is between 5–20 mL/min, and further dose reductions when CrCl <5 mL/min.

The NZ cefotaxime data sheet does not contain information about dosing in haemodialysis, however this is noted in the UK SmPC.

Dosing guidance in the NZF and the Renal Drug Handbook are similar to the NZ cefotaxime data sheet.

Comments:

The threshold for dose reduction for cefotaxime is 20 mL/min in the UK and Australian product information, and 10 mL/min in the NZ data sheet.

Higher doses of cefotaxime maybe used in severe renal impairment as per the cefotaxime NZ data sheet, in comparison to the Australian and UK product information.

Ceftriaxone is different to other cephalosporins, as it undergoes renal and biliary clearance. In the NZ ceftriaxone data sheet, a maximum dose of 2g daily is recommended when CrCl is <10 mL/min.

The Australian PI recommends that blood levels should be monitored in patients with severe renal impairment, including dialysis. If evidence of accumulation from serum levels is evident, then the dose should be decreased accordingly. Monitoring of plasma concentrations is also recommended in the NZ data sheet, however no guidance on levels is provided.

Patients using ceftriaxone who are on dialysis do not require additional dosing following dialysis. Ceftriaxone is not removed by peritoneal or haemodialysis. This information is included in the NZ ceftriaxone data sheet.

Comments:

Monitoring of ceftriaxone plasma concentrations is recommended in patients undergoing dialysis in the NZ data sheet. However, there is no guidance on target plasma concentrations is provided.

3.1.2.4 Fourth generation cephalosporins

The renal dose adjustments for cefepime are similar in the NZ, Australian and UK product information. The dose of cefepime should be adjusted when the CrCl is <50 mL/min.

The NZ cefepime data sheet only has dose adjustments for renal function in adults. However, the UK product information suggests that if children >12 years who are >40kg require renal dose adjustment, adult guidance

can be used. Dosing information for haemodialysis and peritoneal dialysis is provided in the NZ cefepime data sheet.

Comments

Cefepime is highly renally cleared. As a result, renal dose adjustment is required in moderate renal impairment, in addition to severe renal impairment.

3.1.2.5 Fifth generation cephalosporins

The NZ and UK prescribing information for both ceftaroline and ceftolozane (and tazobactam) have the same recommendations for adjustment in renal impairment, respectively.

Dose adjustment should occur when CrCl is <50 mL/min. Information on dosing in end stage renal disease (ESRD) is also included.

3.1.2.6 Summary

Appropriate renal adjustment of cephalosporins in patients with renal impairment, including in dialysis, is important.

Inappropriate overdosing in renal impairment has been highlighted as a risk factor for CIN.

The NZ data sheet dosing recommendations for cefazolin and cefotaxime in patients with severe renal impairment are potentially higher than in the Australian and UK prescribing information.

The cefalexin NZ data sheet does notes caution for use in renal impairment. However, prescribing guidelines (NZF, UpToDate and The Renal Drug Handbook) provide renal dosing recommendations.

The cefazolin NZ data sheet does not include recommendations for dosing in dialysis.

Dosing of antibiotics in renal failure can be challenging. In some clinical situations, there is a balance between risk of accumulation and adverse effects and targeting an effective dose to provide therapeutic benefit.

Renal dosing recommendations for children are not included in some cephalosporin data sheets where renal dose adjustment is provided for adults.

3.2 Published literature

This section includes studies, reviews and case reports identified from the literature.

Articles relating to cefepime were mostly excluded as CIN has already been identified with this cephalosporin and the data sheet includes appropriate information.

3.2.1 Serious central nervous system side effects of cephalosporins: a national analysis of serious reports registered in the French Pharmacovigilance database – Lacroix et al, 2019 [23]

Aim: To review serious CNS (neurological and/or psychiatric) adverse effects from cephalosporins using data from the French pharmacovigilance database.

Method: Serious CNS (neurological and/or psychiatric) ADRs involving a cephalosporin and registered in the French pharmacovigilance data base until 31st December 2017 were extracted. Serious ADR was defined as fatal or life-threatening, requiring hospitalisation or prolongation of ongoing hospitalisation, resulting in persistent or significant disability, other medically important conditions or congenital abnormality or birth defect.

Results: 511 serious reports were identified, representing 755 CNS ADRs. Of these, 52.5% of reports were in males and 62.4% of reports were in patients over 65 years of age. The ADR resulted in a hospitalisation or prolonged hospitalisation in 364 reports, was life-threatening in 61 reports and fatal in 31 reports.

Figure 4 shows the number of ADRs from different cephalosporins. Overall, 20 different cephalosporins were identified. Cefepime (169), was the most frequently reported, followed by ceftriaxone (152), ceftazidime (100), cefotaxime (46) and cefazolin (15).

Figure 4: Number of serious CNS ADRs registered per cephalosporin in the French Pharmacovigilance database

Where information was available from 195 reports, the mean creatinine clearance was 32.9 mL/min and renal impairment present in 87.7% of these reports. There were 128 reports where the patient had a documented history of CNS diseases. The most frequent reported CNS diseases were depression (23.1%), alcoholism (20.3%), epilepsy (16.4%), cognitive disorders (10.2%) and anxious-depressive syndrome (8.6%). There were 254 patients that were exposed to other antibiotics, and 150 patients exposed to other drugs that can affect the CNS.

The most frequently reported serious ADRs reported with cephalosporins are shown in Figure 5. The most frequently reported ADRs included encephalopathy (34.1%), convulsion (27%), confusional state (19.4%), myoclonia (9.4%) and hallucination (6.7%).

Figure 5: The most frequently reported ADRs from reports of cephalosporins and serious CNS ADRs in the French Pharmacovigilance Database

The mean time of onset of CNS ADRs was 7.7 days (standard deviation [SD]: 11.3) after starting a cephalosporin. The mean duration of the ADR was 6 days (SD: 7.4).

Results of an EEG were available in 195 reports and were abnormal for 81%.

Cephalosporin plasma levels were available for 153 patients. Details of these patients are outlined in Table 6. Except for cefotaxime, the majority of plasma levels were above the usual range.

Table 6: Level of exposure to cephalosporin: Number of patients with plasma levels measurements, median plasma levels, number of plasma levels above the standards and number of patients with plasma levels above the standards relate to a renal impairment

Discussion: This study identified reports of serious CNS ADRs of cephalosporins. Signs of encephalopathy (confusional state, hallucination, coma) and/or signs convulsive state (convulsion, myoclonia, status epilepticus) were the main ADRs reported. Results from this study suggest that the elderly are more prone to CNS ADRs, or more frequently reported about as the mean age of patients in the study was 67.7 years.

Results from this study showed that various other cephalosporins have been reported to be associated with CNS ADRs. In addition, that these ADRs are not limited to parenteral administration.

CNS ADRs from cephalosporins can be life threatening and lead to a fatal outcome.

Most patients in the study received doses below the maximum dose in the SmPC, showing that CNS ADRs can occur within normal dose range.

Comments

Previous studies relating to CIN are mostly about cefepime. Regulators, such as the FDA, have communicated about this safety concern with cefepime. Less is known about CNS ADRs related to other cephalosporins.

This review suggests that in addition to cefepime, other cephalosporins can cause CNS ADRs. The risk of neurotoxicity between different cephalosporins may vary. Most reports were associated with cefepime, ceftriaxone and ceftazidime. Cefotaxime and cefazolin had a low number of reports, and cefaclor was one of the least reported cephalosporins, cefalexin had no reports, however the reporting level is likely influenced by use of different cephalosporins in France.

CNS ADRs were reported in patients treated with the normal dose range and were not only due to higher or overdoses.

Renal impairment was present in most of the reports, where this information was available, although this information was missing from a large number of the total reports analysed.

A small number of reports had plasma levels available. Of these, most reported elevated levels, indicating an increased exposure to cephalosporins for these patients. The plasma level that may determine a risk for CIN is unknown. CSF levels were not reported.

Patients were aged over 65 years in more than half of the reports.

A range of CNS ADRs were reported, suggesting that CIN may present as a range of neurotoxic symptoms. However, both encephalopathy and confusional state were reported, though these ADRs could potentially be interchangeable. The sum of the encephalopathy + confusional state reports was greater than the number of seizure reports.

It is not known from this study if a specific cephalosporin is more strongly associated with particular ADRs.

3.2.2 Antibiotic-associated encephalopathy – Bhattacharyya et al, 2016 [35]

Aim: Undertake a comprehensive review of reported cases of antibiotic-associated encephalopathy (AAE) to define the specific clinical features, EEG changes and neuroimaging findings associated with encephalopathy from antibiotic classes and individual antibiotics.

Method: PubMed was searched from beginning of indexing to 16 October 2013. Search terms included were encephalopathy, confusion, delirium, seizure, neuropathy, neurotoxicity, mania, hallucination or psychosis. Articles included must have presented a case report or case series describing patients experiencing alternation of cognition/consciousness after administration of antibiotics and improvement after cessation.

Results: Search yielded 292 articles describing 391 individual cases. Toxicity was reported with 54 different antibiotics from 12 different classes.

Penicillins had 72 reports, followed by cephalosporins with 69 reports. The reports from cephalosporins included cefepime (33), ceftazidime (12), and other (including cefuroxime (5), ceftriaxone (4), cefazolin (3), cefalexin (3) and cefotaxime (2)).

In comparison with other antibiotics, baseline renal insufficiency was particularly common in cases of cephalosporin-associated encephalopathy (72%). The median age for cephalosporin reports was 65 years.

Table 7 shows the clinical characteristics of AAE for penicillins and cephalosporins. Psychosis was much less common in cases of encephalopathy associated with cephalosporins, compared with other antibiotic classes. Seizures were present in 14% of cases overall and were most reported with penicillins (38%) and cephalosporins (35%). Seizures associated with cephalosporin-associated encephalopathy were nonconvulsive in 54% of patients. Myoclonus was found in 41% of cephalosporin reports.

Table 7: Clinical features of penicillins and cephalosporin – associated encephalopathy

Table 8 shows brain MRI and EEG abnormalities in antibiotic-associated encephalopathy. EEG was abnormal in nearly all cases of cephalosporin associated encephalopathy in which EEG was obtained (95%). Of these, both EEG with seizures or epileptiform discharges and EEG with slowing/triphasic waves were identified.

Table 9: Brain MRI and EEG abnormalities in cases of penicillins and cephalosporins – associated encephalopathy

Discussion: Based on the data, three clinical phenotypes of AAE were identified. This are shown in Figure 6.

Figure 6: Types of antibiotic-associated encephalopathy

Type 1 AAE is characterised by onset with days of antibiotic initiation, common occurrence of myoclonus or seizures, abnormal EEG, normal MRI and resolution within days. This is the clinical phenotype seen with cephalosporins and penicillin. It is thought to be caused by disruption of inhibitory synaptic transmission leading to excitotoxicity.

Limitations: This review focused on cases describing altered cognition with antibiotics, as opposed to seizures associated with antibiotics. Reports focusing on seizures with antibiotics may underreport encephalopathy.

Comments:

This review identified signs and symptoms of cephalosporin-associated encephalopathy, which included seizures (including non-convulsive) and myoclonus. A large proportion of cases had baseline renal insufficiency.

Cefepime had the most reports of cephalosporin-associated encephalopathy, followed by ceftazidime. A range of cephalosporins were also reported, although to a lesser extent.

Information from individual case reports was not provided, such as dosing of antibiotics, other medical conditions or medicines, which may have been influential in the outcome.

Identification of antibiotic-associated encephalopathy as a cause of delirium is difficult as patients who are receiving antibiotics may have multiple potential causes of altered cognition. Therefore, antibiotic-associated encephalopathy may be underrecognised.

3.2.3 Antimicrobial exposure and the risk of delirium in critically ill patients – Grahl et al, 2018 [11]

Aim: To determine whether there is an independent association between antimicrobial class exposure in critically ill patients and the daily risk of delirium.

This study talks about encephalopathy and delirium as being similar terms.

Method: The study included adults who received treatment in the medical or surgical ICU for respiratory failure and/or shock between March 2007 and May 2010.

Results: 521 patients were enrolled in the study and 418 patients met the inclusion criteria. Delirium occurred in 74% of patients during their ICU stay. Antimicrobial exposure was found in 318 patients, of which 53% received beta-lactam antibiotics.

From 318 patients who received antimicrobials, the following cephalosporins were identified: 1st generation (cefazolin (10), cefalexin (2)), 2nd generation (cefoxitin (1)), 3rd generation (ceftriaxone (24), cefotaxime (3)) and 4th generation (cefepime (64)).

First, second and third generation cephalosporins were grouped for analysis and demonstrated an association with delirium that was significant (odds ratio (OR): 2.20 (95% confidence interval (CI): 1.28 – 3.79)). Other antimicrobial classes did not have a significant risk (not discussed here). Figure 7 outlines the OR for beta-lactams only.

Figure 7: Delirium risk after antimicrobial exposure using a logistic regression model with cluster sandwich covariance estimator

The risk factors for delirium were delirium on previous day, mechanical ventilation, sepsis and age.

Discussion: The study found that first, second and third generation cephalosporins doubled the odds of delirium after adjusting for baseline co-morbidities, the course of critical care, and other competing

antimicrobials and psychotropic medications risks. The study did not find an association between delirium and cefepime.

Other neurotoxicity symptoms were not included in the study. However, the authors noted that seizures occurred infrequently in the cohort (3%), whereas delirium was much more common.

Limitation: Patients with neurological injuries and neurological conditions were excluded from the study.

Comments:

Delirium is common in critically ill patients treated in the ICU taking antimicrobials.

First, second and third generation cephalosporins doubled the odds of delirium. A higher proportion of patients were on ceftriaxone (24) and cefazolin (10), which may have influenced the result. However, the number of individuals who took a specific cephalosporin and developed delirium is not known.

This study did not find an association with cefepime and delirium in the cohort of patients. This may mean that the risk of encephalopathy was managed appropriately in the cohort. In addition, the risk of such adverse effects (in patients with renal impairment) is well-described in the cefepime prescribing information. There may be greater awareness of the risk of these adverse effects.

Patients with underlying neurological conditions were excluded from the study. These patients may have been more at risk of antimicrobial-induced delirium.

Details about the individuals who experienced delirium, including the dose of antimicrobial administered and renal function, was not provided.

3.2.4 Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure – Martinez-Rodriguez et al, 2001 [16]

Aim: Review cases of nonconvulsive status epilepticus (NCSE) reported in patients with renal failure with ceftriaxone, ceftazidime and cefepime.

Method: EEG database was reviewed from January 1991 to May 2000 for NCSE. A diagnosis was made when continuous or almost continuous epileptiform activity lasting as least 30 minutes was found in a patient with depressed consciousness, agitation or disorientation in the absence of convulsions.

Results: 10 patients were identified who had NCSE who were receiving cephalosporins, 5 male and 5 female, with a mean age of 69 years.

All patients had impaired renal function, 8 had chronic renal failure (including 4 on haemodialysis), and 2 had acute renal failure. One patient also had hepatic failure. Table 9 shows more information about the 10 cases. In all cases, neurological symptoms were slowly progressive, and consisted of depressed consciousness, agitation and disorientation. The mean period between cephalosporin administration and clinical deterioration was 5 days (range 1–10 days). In all patients, cephalosporins were withdrawn and antiepileptic treatment started.

Table 9: Clinical and electroencephalographic features of 10 patients with Nonconvulsive Status Epilepticus associated with cephalosporin therapy

Other causes of seizures, including concomitant medicines, were reviewed but were not thought to be the cause of the reported seizure. No patient had a history of seizures or CNS conditions.

Discussion: In the cases presented in the study, accumulation of cephalosporins in the central nervous system might have led to the development of NCSE. Other causes of seizures were reviewed, however only cephalosporins were temporally related to the appearance of the clinical syndrome.

Comments:

This study reviewed cases of NCSE with third and fourth generation cephalosporins in patients with renal impairment and no previous seizures or CNS disorders.

Clinical findings of NSCE included confusion, myoclonus and agitation.

Only patients with renal failure were included in this study, therefore limited further information about risk in patients with normal renal function.

3.2.5 Cephalosporin-related neurotoxicity: metabolic encephalopathy or non-convulsive status epilepticus? – Triplett et al, 2019 [13]

Aim: To analyse the clinical and EEG findings in patients with cephalosporin-related neurotoxicity (CRN) in a group of hospital patients and the literature. EEG findings have previously reported a metabolic encephalopathy with generalised slowing and triphasic (TW) waves but have also been reported as NCSE.

Method: CRN was identified as an encephalopathy without other obvious cause. Patients were identified from a hospital EEG database between 2002 and 2016. A review of the literature was undertaken with the terms 'cephalosporin', plus 'neurotoxicity', 'status epilepticus', or 'non-convulsive status epilepticus'. EEG was assessed to differentiate between NCSE and TW.

Results: Eleven patients with CRN were identified (cefepime (9), ceftriaxone (2)). All had decreased conscious state and/or confusion. One patient with a history of focal epilepsy and HIV infection had a single tonic-clonic seizure. Six patients had myoclonus. Ten patients had an EEG showing TW, while no EEG was consistent with NCSE.

Table 10 shows the clinical and electrographic features of the patients with CRN.

Table 10: Clinical and electrographic features of 11 patients with cephalosporin-related neurotoxicity

Doses of cephalosporin were more than recommended in 6 patients (including cefepime (5) and ceftriaxone (1). CRN resolved after cessation of the cephalosporin in all patients. Three patients required admission to ICU, with one requiring haemodialysis. No patients who received antiepileptics showed clinical benefit.

From the literature review, 31 articles reported CRN with 37 samples of EEG analysed. Seven EEGs were reported as showing TW consistent with a metabolic encephalopathy and 30 as NCSE.

Discussion: From a group of patients in this study, CRN showed metabolic encephalopathy in most patients, with EEG characteristically revealing generalised slowing and TW. There were more reports of CRN with NCSE compared to TW in the literature. However, these may be incorrectly interpreted as TW.

Accurate EEG interpretation is important given the clinical similarities between NCSE and the encephalopathy generally seen in CRN, including agitation, somnolence and occasionally aphasia. In addition, to ensure appropriate management decisions.

Limitations: Only patients with an EEG receiving cephalosporins were included in the study and may have not included all CRN reports.

Comments:

This study found that cefepime and ceftriaxone can lead to metabolic/toxic encephalopathy. Most patients had renal impairment or were administered the cephalosporin above recommended doses. Seizures were uncommon compared to myoclonus in this group of patients, although the study size was small.

Literature reports more likely showed CRN with NCSE. However, the authors note the difficultly between distinguishing metabolic/toxic encephalopathy and NCSE on EEG.

Patients may present with similar symptoms in metabolic/toxic encephalopathy and NCSE, therefore EEG interpretation is important to guide appropriate management.

3.2.6 Serious neurological adverse events of ceftriaxone – Lacroix et al, 2021 [36]

(This study is related to article 3.2.1, focusing on ceftriaxone)

Aim: To characterise ceftriaxone-induced serious central nervous system (CNS) adverse reactions.

Method: Retrospective descriptive analysis of serious CNS ADR reports in the French pharmacovigilance database from 1995 to 2017.

A literature review of ceftriaxone-induced neurotoxicity was also completed.

Results: A total of 152 serious reports were identified, with 216 CNS ADRs. Most (95.4%) of reports were from hospital clinicians. Women accounted for 55.3% of the reports. The median age from all reports was 74.5 years, and 69.7% of the reports were in patients over 65 years of age.

The ADR led to hospitalisation or prolonged hospitalisation in 73.7% of reports, while deaths and life-threatening ADRs were reported in 7.9% and 10.5%.

Renal function was available for 59 out of the 152 reports (38.8%). Amongst these reports, 44 (74.6%) had renal impairment. The median creatinine clearance was 35 mL/min.

Concomitant administration of other antibiotics was present in 72 patients, and more commonly included fluoroquinolones (34), metronidazole (24) and other beta-lactams (14).

Figure 8 shows the number of serious reports of CNS ADRs related to ceftriaxone per indication.

Figure 8: Number of serious reports of CNS ADRs related to ceftriaxone per indication

The most frequently reported serious neurologic ADRs were encephalopathy (20.8%), convulsions (without other information) (13%), myoclonia (6%), status epilepticus (5.1%), tonic-clonic seizures (1.9%), tonic seizures (0.9%), partial seizures (0.9%), clonic seizures (0.5%) and focal seizures (0.5%). The main psychiatric ADRs reported included a confused state (15.7%), and hallucinations (7.4%). The median time to onset of CNS ADRs was 4 days.

Ceftraixone plasma concentrations were available for 19 patients, of which, 8 were over the toxic level (>100 ug/mL).

EEG results were available in 50 reports (32.9%) and were abnormal in 37 reports. The EEG's specific findings were described in 18 reports, including mainly slow wave discharges, followed by triphasic waves, delta-theta activity or biphasic waves.

Discussion: This review showed the ceftriaxone treatment is associated with life-threatening conditions with serious CNS ADRs. Most reports were in patients aged over 65 years of age.

The number of reports of serious CNS ADRs with ceftriaxone in this review was higher that published in the literature.

Twenty-one cases of ceftriaxone-induced neurotoxicity have been reported and are shown in Table 11. Only 2 of the cases were in patients without renal impairment. CNS ADRs reported included convulsions, myoclonia and signs of encephalopathy.

Table 11: Systematic literature review of neurotoxicity attributable to ceftriaxone

Limitations: Information from spontaneous reporting can be incomplete, under-reporting may occur, and the total number of patients treated is not known.

Comments:

There were more reports of serious CNS ADRs in the French Pharmacovigilance database than reported in the literature. There may be a lack of awareness or identification of these CNS ADRs with ceftriaxone in clinical practice.

Most reports of serious CNS ADRs with ceftriaxone were reported by hospital clinicians, suggesting that these ADRs either mainly occur in hospital or are mainly recognised by hospital clinical staff.

Most reports were in patients over 65 years of age. Only 38.8% of reports had renal function available, however renal impairment was present in a high proportion of these reports.

A range of neurological and psychological ADRs were reported. Encephalopathy, confused state and convulsions were most frequently reported. Some reports were fatal or life-threatening.

The indication for use of ceftriaxone varied among reports and was not limited to meningitis.

Older age and renal impairment were present in a large number of literature case reports.

Confounding factors such as other antibiotics or medicines, medical conditions, concurrent illness and age may make it hard to distinguish between ceftriaxone-induced neurotoxicity and other encephalopathies, especially in the acute hospital setting.

3.2.7 Serious adverse events with novel beta-lactam/beta-lactamase inhibitor combinations: a large-scale pharmacovigilance analysis – Gatti, Raschi & De Ponti, 2021 [37]

Aim: Characterise adverse events of clinical interest reported with ceftolozane-tazobactam (C/T) and ceftazidime-avibactam (C/A) using the FDA Adverse Event Reporting System (FAERS) database.

Method: Observational, retrospective disproportionality analysis of reports recorded between the first quarter of 2015 and the second quarter of 2020. In relation to neurotoxicity with cephalosporins, the following high level groups terms were searched: 'seizures', 'deliria' and 'hallucinations'. Specific preferred terms concerning neurotoxicity were also analysed: 'encephalopathy', 'tremor', 'agitation', 'anxiety', 'cognitive disorder', 'mental impairment', 'altered state of consciousness', 'mental disorder', 'mental status changes', 'myoclonus' and 'neurotoxicity'.

The reporting odds ratio (ROR) with relevant 95% confidence interval (CI) was calculated as a measure of disproportionality. All other drugs/events recorded in FAERS and cephalosporins showing clinical evidence of neurological adverse events were respectively selected as comparator for analysis of designated medical events and neurotoxicity. Traditional criteria for signal detections were used, this was when the lower limit of 95% CI of the ROR was >1, with at least three cases of interest reported.

Results: 654 and 506 reports were identified for C/T and C/A as suspect medicines. From these reports, 11.9% (C/T) and 14% (C/A) included neurological adverse events.

Compared to other selected cephalosporins, C/T exhibited significant ROR for encephalopathy, epilepsy, generalised tonic-clonic seizure and status epilepticus. Increased reporting was found for encephalopathy, mental status changes and tonic convulsion with C/A. After deduplication, encephalopathy with both C/T and C/A, and mental status changes with C/A were retained in at least 3 cases (see Table 12).

Table 12: Selected neurological adverse events reported with ceftolozane – tazobactam and ceftazidime-avibactam showing statistically significant disproportionality

[redacted]

Concomitant renal impairment was found in 28% of cases, while no underlying nervous abnormalities were identified.

Discussion: There was an over-reporting of different serious neurological adverse events (namely encephalopathy and mental status changes) compared to other cephalosporins in patients receiving C/T or C/A. The higher reporting may be related to use at standard (not adjusted for renal impairment) or higher dosing to improve efficacy in severe multi drug resistant infections in clinical practice. Toxic serum concentrations may be more likely to be achieved, therefore leading to a greater risk of neurological AEs.

Comments:

This publication reviewed adverse events reported with ceftolozane and ceftazidime in combination with beta-lactamase inhibitors.

The review suggested a possible signal of encephalopathy with C/T and encephalopathy and mental status changes with C/A.

The number of ADRs relating to neurological adverse events after de-duplication was small, and therefore the significance of the outcome of this study is uncertain. In addition, information about the reports, such as dosing and confounding factors, was not available.

The cephalosporins were analysed in combination, rather than as monotherapy.

3.2.8 Cefepime-induced neurotoxicity: a systematic review – Payne et al, 2017 [18]

Aim: To describe the spectrum of most reported symptoms, risk factors, time frame of onset and resolution of symptoms, patient outcomes and interventions associated with cefepime neurotoxicity.

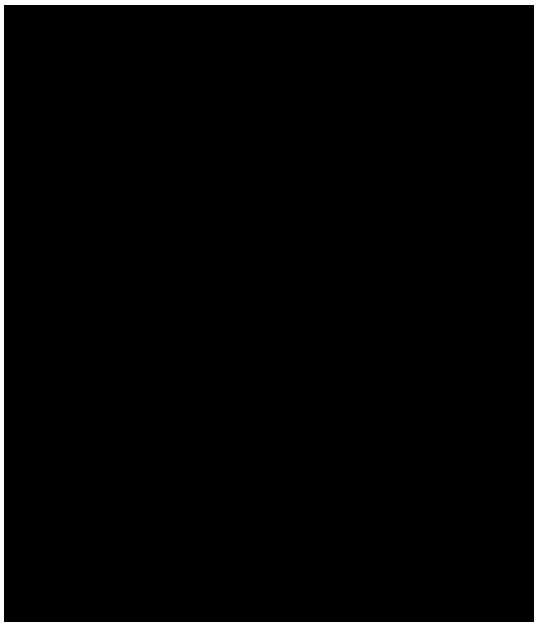
Methods: Literature search between January 1980 and February 2016. Search terms included cefepime, neurotoxicity, encephalopathy, seizures, delirium, coma, non-convulsive status epilepticus (NCSE), myoclonus, confusion, aphasia, agitation and death.

Results: 123 citations identified, 37 were included representing 135 patients (shown in Table 13). Patients were predominantly elderly, had renal dysfunction (80%), and required intensive care (81%).

Table 13: Patient characteristics

Table 14 provides the cefepime dosing, indication and drug concentration characteristics. Almost half (48%) of patients received cefepime regimens that were excessive for their reported renal function, 26% were dosed appropriately and 26% were unable to be assessed. Neurotoxicity was identified a median of 4 days after cefepime initiation.

Table 14: Cefepime characteristics



All patients had an altered mental status. Commonly reported clinical findings were reduced consciousness (47%), myoclonus (42%), confusion (42%), aphasia (15%), seizures (13%) and agitation (11%). Of the 73% of patients with EEG results, all demonstrated abnormalities. Of these, 25% experienced NSCE, 7% had myoclonic status epilepticus, 40% triphasic waves and 39% with focal sharp waves.

Discussion: Table 15 provides a review of the outcomes found in this study. Renal dysfunction and excessive dosing were found to be major risk factors for cefepime neurotoxicity.

Table 15: Cefepime-induced neurotoxicity – a clinical picture

Excessive cefepime exposure, defined by trough determinations greater than 20 mg/L was reported in 12 of the 13 patients. Even with dosage adjustments, high median and excessive trough serum concentrations were seen in the cases analysed. Difficulties in accurately estimating renal function and alterations in PK parameters in the critically ill may explain these findings.

Limitations: Cases analysed may have had confounding factors. There is no accepted definition of an 'acceptable' cefepime trough concentration.

Comments:

This review highlighted risk factors and sign/symptoms of cefepime-induced neurotoxicity from literature cases.

Renal dysfunction and excessive dosing are major risk factors for cefepime-induced neurotoxicity.

It is uncertain what peaklevel of cefepime is associated with neurotoxicity, as there are variations in the literature. Other factors, such as BBB integrity, likely contribute to its neurotoxic potential. Therefore, use of a toxic threshold concentration for cefepime may be of uncertain benefit.

3.2.9 Ceftaroline-associated encephalopathy in patients with severe renal impairment – Martin et al, 2020 [38]

Aim: Retrospective analysis of potential cases of encephalopathy during ceftaroline therapy in patients with severe renal impairment.

Method: Chart reviews were performed for individuals with eGFR of < 30 mL/min that had received 5 or more days of ceftaroline in the years 2010–2018 at a hospital in California.

Results: 28 individuals were included in the study, representing 30 courses of ceftaroline therapy. Two cases of probable encephalopathy and one case of possible encephalopathy were identified (Table 16).

Table 16: Details of case reports of encephalopathy reported with the use of ceftaroline

Case	Gender, age	Renal impairment	Indication	Dose	Symptoms	Management
Case 1	M, 61 yrs	End stage renal disease Haemodialysis	Endocarditis	200mg every 8 hours, increased to 600mg every 12 hours q12 hrly.	Day 30–36: lethargy and myoclonus EEG: are bifrontal and generalised epileptiform discharges and triphasic waves	Discontinued on day 37 Daily dialysis Complete resolution of encephalopathy by day 45
Case 2	M, 87 yrs	Acute kidney injury	Osteomyelitis.	600mg every 8 hours, reduced to 200mg every 12 hours.	Day 20: minimally communicative	Day 22: ceftaroline dose reduced Day 24: dialysis was started and ceftaroline was stopped Day 28: symptoms were much improved

Case 3	M, 61 yrs	Acute kidney injury	Osteomyelitis	600mg every 8 hours	Day 8: lethargic, confusion	Continuous veno-venous renal-replacement-therapy (RRT) was started on day 16 and ceftaroline was discontinued on day 20 Care was complicated by further cardiac arrests and the patient died

Discussion: On review of the cases by the authors, the patients were on higher doses than those approved by the FDA for impaired renal function, either due to a failure to clear blood cultures on lower doses or due to AKI without an adjustment of drug dosing. The onset of encephalopathy coincided with a high likelihood of increasing drug levels, due to changes to renal function.

Although limited by the small study size, the prevalence of encephalopathy was 10% among patients receiving ceftaroline who had an eGFR <30 mL/min.

Limitations: Cases were not investigated systematically for alternative causes of encephalopathy and due to other comorbidities, there were several confounders.

Comments:

Ceftaroline is a fifth generation cephalosporin.

This study identified cases of encephalopathy with ceftaroline in patients with renal impairment before staring therapy or an acute change in renal impairment while on therapy.

The size of the study was small, and only included patients who had renal impairment, which is a known risk factor for CIN.

3.2.10 Case reports

The following section contains case reports identified from the literature.

3.2.10.1 Treatment of cefuroxime-induced neurotoxicity with continuous venovenous haemofiltration – Burgers et al, 2017 [34]

Case report

61-year-old woman presented with 14-day fever, right flank pain and acute on chronic renal insufficiency (serum creatinine 199 umol/L).

She was given cefuroxime IV 1.5g three times daily for suspected urinary tract infection. After 4 days, her creatinine increased to 316 umol/L. Nine days after administration, neurological examination showed a decline in the Glasgow Coma Scale, horizontal nystagmus, myoclonus and tremors. She was admitted to the ICU and diagnosed with cefuroxime-induced neurotoxicity and cefuroxime discontinued.

Continuous venovenous hemofiltration (CVVH) rapidly reduced plasma cefuroxime levels and the patient's neurological symptoms improved.

Comments

This case reported cefuroxime-induced neurotoxicity in worsening renal impairment.

No renal dose adjustment was undertaken even though serum creatinine had increased. This likely was influential in this case.

3.2.10.2 Cefazolin induced seizures in haemodialysis patients – Arkaravichien, Tamungklang and Arkaravichien, 2006 [39]

Case report

29-year-old woman admitted to hospital and started on cefazolin 2g IV every 8 hours. She had a history of end stage renal disease and was on haemodialysis.

She was treated with cefazolin for 25 days. On day 14, she developed generalised tonic-clonic seizure with aura. Neurological exam was performed but no neurological deficit was detected. Seven days later the patient developed another generalised tonic-clonic seizure and was treated with diazepam and phenytoin. Four days later she developed a third episode of generalised tonic-clonic seizure.

Cefazolin was identified as the cause for the seizures and discontinued. No more seizures were noted.

Discussion

The dosing of cefazolin in this case was inappropriately high, and in combination with renal impairment, led to cefazolin accumulation, and subsequent crossing of the blood brain barrier into CSF and brain.

Cefazolin-associated seizures have been previously reported. They were associated with patients with impaired renal function receiving high dose cefazolin for a prolonged period and who developed generalised tonic-clonic seizures.

Comments:

Long duration of antibiotic treatment in renal impairment may lead to increased accumulation of cefazolin, which may lead to seizures.

If the clinical scenario requires long-term antibiotic therapy, renal function should be monitored, and dose adjustments made as appropriate.

3.2.10.3 Seizures associated with high cerebrospinal fluid concentrations of cefazolin – Bectel, Slaughter and Moore, 1980 [40]

Case reports

60-year-old woman with impaired renal function, administered gentamycin and cefazolin (1.5g IV every 4 hours). On day 12, she had a generalized tonic-clonic seizure. Serum and CSF concentrations obtained one day later were 470 and 64 micrograms/mL, respectively.

70-year-old man with impaired renal function administered cefazolin (1g every 12 hours, increased to 6-hourly). Two days later the patient had 2 tonic-clonic seizures. Serum and CSF concentrations 8 hours after the last dose were 360 and 34 micrograms/mL, respectively.

67-year-old woman with renal vein thrombosis was given gentamycin and cefazolin (2g every 6 hours). On day 8, the patient had 2 tonic-clonic seizures. Serum and CSF levels were measured and were 1000 and 106 micrograms/mL, respectively.

Discussion

Patients with renal failure may have high CSF concentrations of cefazolin, which may contribute to seizures.

Comments

CSF concentrations of cefazolin may be elevated when cefazolin is not dose adjusted in renal impairment.

A study in mice by Sugimoto et al (2003) found that cefazolin, out of the cephalosporins studied, had the most anticonvulsive activity [22]

3.2.10.4 De novo absence status epilepticus of late onset (DNASLO) precipitated by oral treatment with cefuroxime: description of an ambulatory case – Fernandez – Torre et al, 2018 [41]

Case report

79-year-old woman admitted to hospital after 48 hours of behavioural abnormalities and disorientation. She had been taking oral cefuroxime for acute media otitis the week before.

On neurological examination, she was confused and disorientated to time, with poor spontaneous speech and a mild tremor in both upper limbs. An EEG revealed frequent and recurrent generalised paroxysms of spike-wave complexes, intermixed with brief periods of normal background activity, in keeping with the diagnosis of de novo absence status epilepticus of late onset (DNASLO).

Cefuroxime was discontinued and 24 hours later, the patient returned to normal with a normal EEG.

Discussion

DNASLO is a subtype of NCSE. Renal function in this patient was normal.

Previous studies have reported 4 cases of cefuroxime-induced encephalopathy. The EEG in all patients showed generalised slowing, but epileptiform activity was absent. The clinical picture was acute and reversible.

Comments:

A high level of suspicion for neurotoxicity should be taken in cases of unexplained confusion in adults, especially in the elderly, taking cephalosporins.

3.2.10.5 Jerky movement with ceftazidime: A case of ceftazidime-induced neurotoxicity with a review of the literature – Al-Sadawi et al, 2019 [17]

Case report

78-year-old male started on ceftazidime 2g IV every 8 hours for pyelonephritis. His eGFR reduced from 63 mL/min to 35 mL/min.

After 3 days of treatment, he developed jerky movements of the jaw and both upper extremities. Ceftazidime was discontinued. After 48 hours, his symptoms improved.

Discussion

Ceftazidime was not adjusted based on the creatinine clearance. Prevention, by appropriate dosing in renal impairment, is important.

Comments:

The patient's condition improved 48 hours after discontinuation of the antibiotic, suggesting that his symptoms were caused by the antibiotic rather than the underlying infection.

3.2.10.6 Probable nonconclusive status epilepticus with the use of high dose continuous infusion ceftazidime – Collins et al, 2016 [21]

Case report

64-year-old man presented to hospital with neutropenic fever.

Ceftazidime 8 gram/day via IV continuous infusion and IV colistin was initiated. His CrCl was 126 mL/min. On hospital admission day 4, the patient developed septic shock and was admitted to the ICU. Ceftazidime was increased to 16 g/d and colistin continued. His CrCl had reduced to 88 mL/min. On hospital day 8, the dose of ceftazidime was increased to 19.2 g/d due to improved renal function (117 mL/min).

On hospital day 9, the patient experienced agitation. Computed tomography (CT) scan revealed a small subarachnoid haemorrhage (SAH). On hospital day 11, the patient experienced new-onset facial jerking and myoclonus. An EEG revealed NCSE. He was administered anti-convulsants. Ceftazidime was discontinued on day 12. Renal function had declined to 39 mL/min.

Discussion

There have been prior reports neurological adverse effects with ceftazidime. Chow et al, 2005 reviewed 12 cases of ceftazidime-induced neurotoxicity. All 12 patients were in acute or chronic renal failure. Most (91%) patients exhibited confusion, 50% myoclonus and one patient experienced a seizure. On EEG, 75% were in NCSE although none experienced generalised seizures during assessment. Symptoms resolved in all patients on discontinuation of ceftazidime.

Other potential causes of neurotoxicity in this case include SAH on CT and the use of colistimethate sodium. The events in the case report may have occurred due to multiple factors.

The authors note that it may be prudent to avoid high dose continuous infusions of beta-lactam antibiotics in patients with neurological conditions associated with an increased potential for seizure activity. This case also highlights a specific population that may benefit from beta-lactam therapeutic drug monitoring.

Comments:

Administration of cephalosporins at high doses by continuous infusion may be a risk factor for neurotoxic effects, particularly in the presence of other risk factors such as CNS disease, renal impairment and concomitant medicines known to contribute to neurotoxicity.

3.2.10.7 Ceftazidime encephalopathy developed without elevation of cerebrospinal fluid concentration of ceftazidime: A case report of two cases – Toda et al, 2022 [42]

Case reports

Case 1

80-year-old male with end stage renal disease (ESRD), on both peritoneal dialysis and haemodialysis. Six days after starting ceftazidime (1g every 12 hours), he developed altered consciousness, dysarthria and myoclonic movements in bilateral upper extremities. EEG showed triphasic waves suggesting drug-induced encephalopathy, and ceftazidime was discontinued.

Serum concentration of ceftazidime was markedly increased on the day that symptoms developed; however, the CSF concentration was less than 0.1 ug/mL.

Case 2

88-year-old male with CKD. Five days after starting ceftazidime (1g ever 12 hours), he developed altered consciousness. Ceftazidime-encephalopathy was clinically suspected, and the antibiotic was discontinued.

The serum level of ceftazidime was markedly increased; however, the CSF concentration was within the therapeutic range.

Discussion

Ceftazidime encephalopathy is caused by the high serum concentration of ceftazidime, especially in patients with renal impairment, who received repeated administration of ceftazidime. The patients in the 2 cases presented developed ceftazidime encephalopathy without the elevation of CSF concentrations.

There could be an alternative mechanism occurring that causes encephalopathy in patients with high plasma concentration levels of ceftazidime, but low CSF levels. Ceftazidime upregulates TNF-alpha, which then increases quinolinic acid. Quinolinic acid may then be transported into the brain and acts as an excitatory transmitter of NMDA receptors, causing neurotoxicity. However, more research is needed in this area.

Review of the 16 literature cases of ceftazidime encephalopathy is shown in Table 17. Of these, 13 cases had underlying renal impairment, including 7 cases where the patient was on renal replacement therapy due to ESRD.

Table 17: Case reports of ceftazidime encephalopathy

[redacted]

Comments:

This article includes 2 reports of ceftazidime-induced encephalopathy, where CSF levels were in the normal range, but plasma levels were elevated.

The author proposed an alternative mechanism for neurotoxicity.

There are several case reports of ceftazidime-induced encephalopathy in the literature, most often in patients with renal failure.

Myoclonus was frequently reported.

3.2.10.8 Ceftazidime/avibactam neurotoxicity in an adult patient with normal renal function – Pingue et al, 2020 [43]

Case report

70-year-old woman with a history of brain injury experienced neurological complications from ceftazidime/avibactam, without renal impairment.

She was administered 2.5g every 8 hours for sepsis. At day 6, she experienced focal seizures and progressive impaired awareness. Plasma and CSF analysis was performed. CSF analysis showed a moderate blood-CSF barrier damage. Ceftazidime levels were 36.9 mg/L in plasma and 0.26 mg/L in the CSF. Brain magnetic resonance imaging revealed diffusely thickened and hyperintense leptomeninges compatible with meningeal inflammation.

On day 15 the antibiotics were discontinued, and 2 days later the patient showed an overall improvement. Two weeks after discontinuation, the brain CT showed resolution of meningeal involvement.

Discussion

This patient experienced severe encephalopathy that occurred after the initiation of the ceftazidime/avibactam and resolved on discontinuation. Brain MRI identified meningeal inflammation, which improved after suspending the drug.

An increase in blood-CSF barrier permeability may have led to neurotoxic levels in the CNS. This could have been caused by the sepsis. Meningeal inflammation could also be due to a drug-induced aseptic meningitis. Pathogenic mechanisms of drug-induced aseptic meningitis include immune-complex pathologies, hyper-sensitivity reactions or direct meningeal irritation.

Comments:

This author presents a case of neurological complications with ceftazidime/avibactam and discusses how meningeal inflammation may lead to increased levels of ceftazidime in the CNS.

The author does not discuss the patient's history of brain injury; however, this could have increased the patient's susceptibility to neurotoxic effects of ceftazidime.

3.2.10.9 Additional case reports of ceftriaxone-induced neurotoxicity in the literature

Table 27 shows additional case reports of ceftriaxone-induced neurotoxicity in the literature.

Comments

Three cases presented in Table 18 have ESRD or are on dialysis and are taking the recommended maximum dose of 2g of ceftriaxone when CrCl <10 mL/min. However, they still experienced CIN.

Table 18: Literature case reports of ceftriaxone-induced neurotoxicity

Author(s)	Gender, age	Dose	Indication	Liver/renal impairment	Neurotoxicity ADRs	Management	Comments
Anto et al [25]	F, 73 yrs	2g daily	Perioperative prophylaxis Craniotomy for multicentric glioma	n/a	Encephalopathy post-operatively (delayed wakening)	Ceftriaxone stopped, gradual improvement in symptoms	Cerebrovascular disease, meningitis, and cerebral contusion are neurological conditions that have been reported to predispose to ceftriaxone induced encephalopathy.
Jadot et al 2021 [30]	M, 64 yrs	2g 12 hrly	Endocarditis	Liver impairment CrCl 37 mL/min (baseline)	Day 22: acute encephalopathy	Ceftriaxone discontinued; symptoms improved 3 days after.	Developed acute kidney injury while on therapy, requiring dialysis EEG: toxic encephalopathy without epileptiform discharges Elevated CSF ceftriaxone concentrations (29.9 mg/L)
Nishoka et al, 2022 [32]	F, 78 yrs	1g daily	Urinary tract infection	Haemodialysis	Day 9: drowsy	Day 10: ceftriaxone stopped as antibiotic course complete	Elevated levels of ceftriaxone: Plasma ceftriaxone was taken after stopping: 63.6 ug/mL (day 1), 12.8 ug/mL (day 4). CSF ceftriaxone level: 10.2 ug/mL (day 2).
Futagi et al 2022 [44]	M, 84 yrs	2g daily	Pneumonia, pyelonephritis	One kidney	Day 8: tonic-clonic seizure	Ceftriaxone discontinued day 8 as course completed	Hepatic dysfunction in combination with a solitary kidney may synergistically increase blood levels of ceftriaxone
Pires et al 2009 [33]	F, 60 yrs	1g daily	Urinary tract infection	Creatinine: 177 umol/L	Day 4: altered mental status, progressive apathy, somnolence	Ceftriaxone discontinued; symptoms improved within 3 days	History of seizure on carbamazepine and cerebrovascular disease
Onogi et al 2021 [45]	M, 78 yrs	2g daily	Sepsis	End stage renal disease	Day 8: reduced consciousness Day 11: myoclonic jerks	Ceftriaxone discontinued; symptoms resolved	Considering the protein binding rate of ceftriaxone, hemoperfusion is preferable to haemodialysis for directly eliminating serum ceftriaxone
Onogi et al 2021 [45]	M, 38 yrs	2g daily	Enteritis	End stage renal disease	Day 4: altered mental state, myoclonic jerks	Ceftriaxone discontinued, and symptoms resolved	EEG: Triphasic waves

3.2.11 Summary of literature

Lacroix et al 2019 provided a review of serious CNS ADRs of cephalosporins from pharmacovigilance reports. A review of such ADRs had not previously been analysed; however, the outcome of this study suggested that multiple cephalosporins may cause serious CNS ADRs.

Cefepime, ceftriaxone and ceftazidime were most frequently associated with CIN, followed by cefazolin and cefuroxime. The number of reports for cefotaxime was lower than other third generation cephalosporins, but this may reflect lower usage. Cefalexin and cefaclor were included in very few reports. The fifth generation cephalosporins ceftaroline and ceftaroline were each represented by one study.

CIN was reported as both an encephalopathy and NCSE, and patients may vary in their presentation. Depressed consciousness and confusion may be present in encephalopathy and NCSE. CIN may also present as myoclonus. Patients may also experience a convulsive seizure; however, this may be less common than symptoms relating to mental state changes. Agitation was also reported in some cases. EEG monitoring may be used to identify whether symptoms correlate to seizure activity.

The symptoms of CIN were not specific to a particular cephalosporin. Myoclonus was reported in several ceftazidime case reports. There were multiple case reports of cefazolin-induced generalised tonic-clonic seizures.

The indications for use of cephalosporins varied in the case reports and were not limited to meningitis (where meningeal inflammation is present).

CIN may be hard to diagnose due to multiple risk factors for encephalopathy/delirium that may present with similar symptoms.

Renal insufficiency (mostly CKD) and older age were common themes in the literature. An abnormal EEG was also a common finding.

3.3 Spontaneous reporting

3.3.1 CARM reports

Table 19 outlines reports of CIN up to 31 October 2022, received by the Centre of Adverse Reactions Monitoring (CARM) for approved and available cephalosporins in NZ.

Reports are only included if the cephalosporin was reported as a suspect medicine and where the symptoms could relate to CIN, including mental status changes.

There were no reports for ceftaroline and ceftolozane.

Table 19: New Zealand case reports, where a cephalosporin was listed as a suspect medicine and neurotoxic adverse effects were reported

	CARM ID	Reaction	Dose/route (if available)	Cephalosporin start/stop date	Age, gender	Other medications and medical conditions	Seriousness	Relationship
Cefazolin	58339	Stridor, convulsions, hypotension, hypoxia	[redacted] IV	[redacted]	F, 47 yrs	Concomitant: Ceftriaxone, propofol, fentanyl, ondansetron.	[redacted]	[redacted]
	77512	Convulsions grand mal, cardiac arrest	[redacted] IV	[redacted]	F, 67 yrs	Co-suspect: rocuronium, fentanyl, alfentanil, propofol	[redacted]	[redacted]
	86695	Twitching, eyes rolling, headache, diplopia, nystagmus	[redacted] IV	[redacted]	M, 22 yrs	Co-suspect: propofol, sevoflurane, fentanyl, ondansetron	[redacted]	[redacted]
	97392	Convulsions grand mal	[redacted] IV	[redacted]	F, 84 yrs	Concomitant: metoprolol, nitrofurantoin, vitamin D, paracetamol	[redacted]	[redacted]
	105241	Agitation, stridor, face oedema	[redacted] IV	[redacted]	M, 2 yrs	Concomitant: paracetamol, codeine	[redacted]	[redacted]
	122558	Urticaria, agitation, dyspnoea	IV	[redacted]	M, 57 yrs	Concomitant: gentamicin, morphine, bupivacaine, chlorhexidine	[redacted]	[redacted]
	137985	Myoclonus, myoclonus jerks, hiccup	[redacted] IV	[redacted]	M, 48 yrs	Nil	[redacted]	[redacted]
Cefalexin	123136	Confusion, delirium	[redacted] PO [redacted]	[redacted]	F, 88 yrs	Concomitant: citalopram, paracetamol, omeprazole, furosemide, aspirin, allopurinol, Vit D, iron, citalopram, metoprolol, isosorbide, quinapril gabapentin.	[redacted]	[redacted]
	136282	Convulsions, cramp abdominal, nausea, diarrhoea, fever	[redacted] PO [redacted]	[redacted]	F, 16 yrs	Nil	[redacted]	[redacted]

Cefuroxime	24559	Hallucination, extrapyramidal disorder	[redacted] IV	[redacted]	F, 66y rs	Co-suspect: morphine Concomitant: madopar, propranolol, ascorbic acid [redacted]	n/a	[redacted]
	26025	Confusion, somnolence, hallucination, speech disorder	[redacted] IV	[redacted]	M, 67 yrs	Concomitant: ranitidine, vitamin B, isradipine, calcitriol [redacted]	n/a	[redacted]
	26764*	Muscle contractions involuntary	[redacted] PO	[redacted] 4	M, 35 yrs	Co-suspect: cefotaxime Concomitant: erythromycin, ascorbic acid, vitamin B [redacted]	n/a	[redacted]
	52754	Coma	[redacted] IV [redacted]	[redacted]	F, 92 yrs	Co-suspect: sodium valproate, phenytoin	[redacted]	[redacted]
	57256	Confusion, rash pruritic	[redacted] IV [redacted]	[redacted]	F, 35 yrs	Concomitant: metronidazole, paracetamol, tramadol [redacted]	[redacted]	[redacted]
	87469	Disorientation	[redacted] PO	n/a	M, 56 yrs	Concomitant: simvastatin, fluoxetine, acetylsalicylic acid, metoprolol	[redacted]	[redacted]
Cefaclor	22512	Lethargy, confusion, myalgia	[redacted] PO	n/a	F, 27 yrs	Nil	n/a	[redacted]
	33509	Hyperkinesia, insomnia, aggressive reaction	[redacted] PO daily	[redacted]	M, n/a	Nil	n/a	[redacted]
	50548	Confusion, dysarthria	n/a	n/a	M, 59 yrs	Co-suspect: promethazine Concomitant: adrenaline, hydrocortisone, felodipine	[redacted]	[redacted]

Cefotaxime	26764*	Muscle contractions involuntary	[redacted] IV	[redacted]	M, 35 yrs	Co-suspect: cefuroxime Concomitant: erythromycin, ascorbic acid, vitamin B [redacted]	n/a	[redacted]
	105295	Convulsions	[redacted]	n/a	F, 8 yrs	Nil	[redacted]	[redacted]
Ceftazidime	28172	Confusion, muscle contractions involuntary, somnolence	[redacted] IV [redacted]	[redacted]	F, 50yrs	Concomitant: ascorbic acid, vitamin B, prednisone, ranitidine [redacted]	n/a	[redacted]
	136000	Malaise, shaking	[redacted] IP (intraperitoneal)	[redacted]	M, 69yrs	[redacted]	[redacted]	[redacted]
Ceftriaxone	107950	Delirium consciousness decreased, convulsions	[redacted] V [redacted]	[redacted]	F, 71 yrs	Concomitant: ciprofloxacin, amlodipine, sodium valproate, citalopram [redacted]	[redacted]	[redacted]
	110187	Encephalopathy, renal failure acute, pulmonary odema	[redacted] IV [redacted]	[redacted]	F, 66 yrs	Suspect: amoxillin, acyclovir, phenytoin. Concomitant: salbutamol	[redacted]	[redacted]
Cefepime	98398	Encephalopathy, renal failure aggravated, myoclonus	[redacted] IV [redacted]	[redacted]	F, 70yrs	Concomitant: morphine, diazepam, gabapentin [redacted]	[redacted]	[redacted]
	108616	Confusion, delirium, tremor	[redacted] IV [redacted]	[redacted]	M, 85 yrs	Nil	[redacted]	[redacted]

* Report 26764 had cefuroxime and cefotaxime as co-suspect cephalosporins.

Seven reports were identified for cefazolin, including 3 reports where convulsions were reported. Most of these reports [redacted] Myoclonus was reported by a 48-year-old male, with no [redacted] other medicines, after one dose of cefazolin was administered [redacted] There has been another report of cefazolin with twitching and nystagmus, however multiple other medicines were administered at the same time. Two reports of agitation were also identified.

Convulsions was reported in a 16-year-old female one day after [redacted] cefalexin [redacted] Confusion and delirium were reported in an older female after taking cefalexin [redacted]

Potential symptoms of encephalopathy, such as confusion and hallucination, were noted in 2 cases with cefuroxime. In both cases, the age of the patient was >65 years [redacted]. Two cases of confusion were also reported with cefaclor.

'Muscle contractions involuntary' was reported in a 35-year-old male, who had been administered cefotaxime IV followed by cefuroxime oral. Both medicines were listed as suspect medicines. [redacted]

'Convulsions' was reported in an 8-year-old female with cefotaxime, however there were no other details provided in the report.

There were 2 cases of myoclonus-like symptoms reported in patients [redacted].

Two reports were identified for ceftriaxone. One case was in an elderly woman [redacted] and the reported terms included delirium, consciousness decreased (which may represent encephalopathy) and seizures. Another report of encephalopathy [redacted] was reported with use of other antibiotics/antivirals.

Encephalopathy was also reported in 2 cases with cefepime, [redacted] One case included a patient who was taking cefepime [redacted]

[redacted]

Comments

CARM has received several reports that may be related to CIN.

Cefazolin had the most reports (7), including reported ADRs of convulsions and myoclonus. Cefazolin may be more widely used than other parenterally administered cephalosporins, which may correspond with the higher number of reports seen with this cephalosporin. Cefazolin is also used in perioperative prophylaxis, such as orthopaedic surgery. Elderly patients with renal impairment may be exposed to cefazolin during and after surgery for hip and knee replacements. There is no information about neurotoxicity in section 4.4 or 4.8 of the cefazolin data sheet.

Cefuroxime had the second highest number of reports (6) and is also commonly used in hospital for treatment of urinary, respiratory, and abdominal infections. Adverse effects in the reports were relatively non-specific and it is uncertain if symptoms reported were related to an encephalopathy or not. However, most included mental status changes. [redacted] Muscle contractions involuntary was reported in one case, which listed IV cefotaxime and oral cefuroxime as suspect medicines. Coma was reported in a patient also taking sodium valproate and phenytoin (also suspect medicines). In this case, [redacted] may have been a risk factor, in addition older age (92 years). There is no information about neurotoxicity in section 4.4 or 4.9 in the NZ cefuroxime IV or oral data sheet.

Confusion was reported in 2 cases with cefaclor. Confusion is listed in the NZ cefaclor data sheet.

In comparison with other cephalosporins, the neurotoxic effects of cefepime are well-described in the data sheet, with warnings about encephalopathy, seizures, myoclonus and other neurological effects.

Convulsions and encephalopathy have been reported with ceftriaxone. However, unlike the Australian and UK prescribing information, there is no information about these ADRs in the NZ ceftriaxone data sheet.

A range of possible symptoms of CIN have been reported with most cephalosporins in NZ. However, the number of reports is low, suggesting that the ADR is rare. Confusion or altered mental state may represent NCSE, however it might not be reported as NCSE if EEG monitoring is not undertaken.

Different cephalosporins may be more likely to cause certain neurotoxic effects. Convulsions were reported with cefazolin, cefalexin, cefotaxime and ceftriaxone. Myoclonus was reported with cefepime, cefotaxime, cefazolin, cefuroxime/cefotaxime and ceftazidime. However, there are only a small number of reports to review this.

[redacted] and older age were present in several reports.

Lack of recognition of CIN could lead to underreporting.

3.3.2 VigiLyze

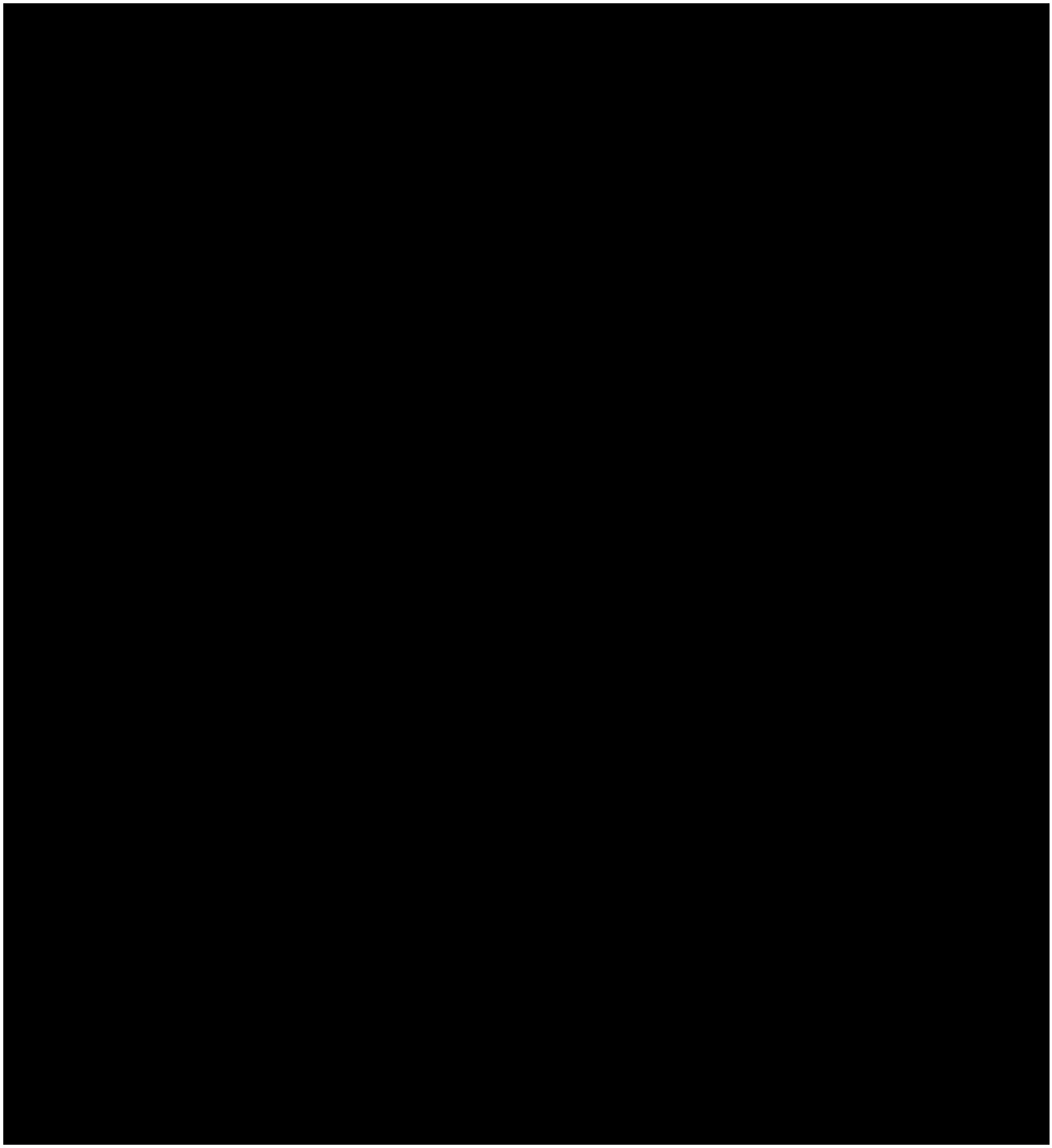
On 28 October 2022, the VigiLyze data base was reviewed for potential CIN reports.

Figure 9 outlines the number of reports for the preferred terms (PTs) 'encephalopathy', 'seizures', 'depressed level of consciousness', 'myoclonus' and 'confusional state', for each cephalosporin.

Comments

These PTs were chosen based on the commonly-reported symptoms of CIN in the literature.

Figure 9: Number of reports in VigiLyze for the preferred terms 'encephalopathy', 'seizures', 'depressed level of consciousness', 'myoclonus' and 'confusional state', by cephalosporin



Source: WHO VigiLyze, accessed 28 October 2022

Comments:

[redacted]

3.4 Regulatory information

3.4.1 Communication

Cefepime- and ceftriaxone-induced neurotoxicity have been communicated by several international regulators.

3.4.1.1 Food and Drug Administration (FDA)

In 2012, the FDA published a drug safety communication about cefepime and risk of seizure in patients not receiving dosage adjustment for kidney impairment [46].

The FDA reported that there had been cases of a specific type of seizure called nonconvulsive status epilepticus associated with the use of cefepime. Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment, although some cases occurred in patients receiving dosage adjustment appropriate for their degree of renal impairment. In most cases, the seizures were reversible and resolved after discontinuing cefepime and/or after haemodialysis [46].

From 1996 to February 2021, the FDA identified 59 cases of NCSE during cefepime administration, including 16 fatal cases. Of these 59 cases, 56% involved patients >65 years of age. Renal dysfunction was present in 58 patients. In 56 patients, the cefepime dose was not appropriately adjusted for renal impairment, as recommended the product label (data sheet). NCSE resolved in 43 patients. Of the 16 patients who died, 13 deaths were caused by concurrent illness. From the 3 remaining cases, one involved a patient with central nervous system disease and a ventriculoperitoneal shunt, one had concomitantly elevated amoxicillin levels and one had insufficient data [46].

To minimise the risk of seizures, the FDA advised that health care professionals should adjust the dosage of cefepime in patients. Caregivers who notice symptoms of NCSE in a patient receiving cefepime should seek medical attention right away. Symptoms include altered mental status, confusions and decreased responsiveness [46]

3.4.1.2 European Medicines Agency

The Pharmacovigilance Risk Assessment Committee (PRAC) discussed ceftriaxone and encephalopathy at the October 2020 meeting [47].

Upon the available evidence from non-clinical data, post-marketing setting, clinical trials and literature, and taking into account the plausible biological mechanism, the PRAC agreed that the ADR should be added to the product information for ceftriaxone [47].

The PRAC recommended adding the following to the ceftriaxone EU SmPC product information:

4.4. Special warnings and precautions for use

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8), particularly in elderly patients with severe renal impairment (see section 4.2) or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

4.8. Undesirable effects

SOC Nervous system disorders Frequency 'rare': Encephalopathy

Package leaflet

Possible side effects: Treatment with ceftriaxone, particularly in elderly patients with serious kidney or nervous system problems may rarely cause decreased consciousness, abnormal movements, agitation and convulsion

3.4.1.3 Health Canada

Ceftriaxone

In early 2021, Health Canada issued a summary safety review of ceftriaxone containing products, assessing the potential risk of encephalopathy. The review was triggered by a study published in the Journal of Neurological Sciences, by Lacroix et al (see section 3.2.1 of this report) [48].

Health Canada reviewed 29 cases (5 Canadian and 24 international) of encephalopathy reported with the use of ceftriaxone. The 24 international cases included 18 reported to the Canada Vigilance database and 6 in the literature. Of the 29 cases, 17 were found to be possibly linked to the use of ceftriaxone. Health Canada also assessed 5 studies and 3 review articles from the published scientific literature [48].

Health Canada's review of the available information concluded that there is a possible link between the use of ceftriaxone and the risk of encephalopathy. They recommended updates to the ceftriaxone product labels (data sheets) [48].

Cephalosporins

Health Canada is currently reviewing the cephalosporin product class and the potential safety issue of seizures [49].

This review was triggered by the FDA. The FDA labels for the cephalosporin class of medicines include a warning for neurological adverse effects. The outcome of this review is ongoing [49].

3.4.1.4 Therapeutic Goods Administration (TGA – Australia)

The TGA published a safety update in December 2021, for ceftriaxone and the risk of hepatitis and encephalopathy. Up until 16 November 2021, the TGA had received 3 reports of encephalopathy for ceftriaxone [50].

Heath professionals were advised that the product information for ceftriaxone had been updated to include a warning about encephalopathy, particularly in older patients with underlying renal impairment or CNS disorders [50].

The following information was added to the Australian ceftriaxone PI:

Section 4.4

'Encephalopathy has been reported with the use of ceftriaxone, particularly in elderly patients with severe renal impairment or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.'

Comments:

Medsafe have not previously communicated about this potential safety issue.

The ceftriaxone data sheet currently does not contain any information about encephalopathy.

4 CONCLUSIONS

Cephalosporins are a class of antibiotics commonly used in NZ.

Cefaclor and cefalexin are administered orally and are mainly used in primary care. A higher number of people have been dispensed cefalexin than cefaclor from 2018 to 2020. Other available cephalosporins are administered via injection and are used in hospital following local guidelines. There are a few clinical exceptions where these cephalosporins may be administered in the community.

Choice and dose of a cephalosporin depends on several factors, including the type and severity of the infection, antimicrobial susceptibility, and the patient's renal function. Third, fourth and fifth generation cephalosporins have an extended spectrum of antimicrobial activity. These cephalosporins are used in the treatment of severe infections in critically ill patients. Except for cefaclor, all cephalosporins require a dose reduction in renal impairment.

Neurotoxicity has been reported with beta-lactam antibiotics, such as penicillin and cefepime. Neurotoxicity with other beta-lactams, such as other cephalosporins, is increasingly recognised.

Encephalopathy (symptoms of mental status changes), myoclonus and seizures have been reported in cases of CIN. Such manifestations may vary between different cephalosporins and between individuals, shown through literature case reports and spontaneous reporting.

CIN may be caused by a direct toxic effect in the CNS and/or inhibition of $GABA_A$ receptor. Diagnosis of CIN is challenging, as there are multiple factors that may cause changes in mental status and/or seizures in a patient.

[redacted] Most cephalosporins require a reduced dose when used in patients with renal impairment due to the risk of accumulation. Recommendations for renal dose adjustment of cephalosporins are included in data sheets, however slight variations have been noted in comparison with some international product information. In addition, renal dosing recommendation are often limited to adults, however cephalosporins are also used in children.

Most reports of neurotoxicity with cephalosporins were from case reports and spontaneous reporting. Certain cephalosporins were more frequently reported than others, which may indicate a higher risk of CIN if there is a causal association. There are multiple factors that may influence reporting of different cephalosporins, including pharmacokinetic properties of the drug themselves and risk factors in the individual using the antibiotic. It is likely that reporting of CIN is the result of multiple factors.

Information on CIN varies across the NZ cephalosporin data sheets. It is included in section 4.4 of the cefotaxime, ceftazidime, ceftaroline and cefepime data sheets. Neurotoxicity symptoms have been reported with cefazolin and ceftriaxone in NZ, however these ADRs are not currently listed in the data sheets.

CIN has been reported with cephalosporins internationally. The FDA labels include a warning for neurotoxicity for the cephalosporin class.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether there is evidence for an association between the entire cephalosporin class and neurotoxicity?
  - If no, is there evidence for an association between a specific generation of cephalosporin and neurotoxicity, or
  - Is there evidence for an association for a specific cephalosporin and neurotoxicity?

- If there is evidence for an association (for the entire class, a specific generation, or a specific cephalosporin):
  - Does the Committee consider that a warning should be included in section 4.4 for all products and related to neurotoxicity in general or specific separate warnings for encephalopathy and/or seizures
  - If a warning is desirable, should it include risk factors, and management (for example EEG monitoring and discontinuation of treatment),
  - Should these terms be included in section 4.8: encephalopathy, delirium, confusion, depressed level of consciousness, agitation, hallucinations, disorientation, tremor, myoclonus, seizures, NCSE.

- The risk of neurotoxicity appears to be linked with renal function. An inconsistency in recommendations of renal dosing has been identified across countries. Does the Committee consider the inconsistences to be important and require adjustment.

- Does the topic require further communication, other than MARC's remarks in Prescriber Update?

6 ANNEXES

Annex 1: Neurological effects of cephalosporins listed New Zealand, Australia and UK product information.

Annex 2: Adult renal dosing information for cephalosporins in New Zealand, Australia and UK product information, and prescribing resources.

7 REFERENCES

1. Best Practice Advisor centre (BPAC). 2011. Appropriate use of cephalosporins. URL: https://bpac.org.nz/BPJ/2011/december/cephalosporins.aspx: (accessed 18 October 2022).
2. De Rosa M, Verdino A, Soriente A, et al. 2021. The Odd Couple(s): An Overview of Beta-Lactam Antibiotics Bearing More Than One Pharmacophoric Group. *International Journal of Molecular Sciences* 22(2): 617. URL: https://www.mdpi.com/1422-0067/22/2/617 (accessed 14 November 2022).
3. A Letourneau. 2022. Beta-lactam antibiotics: Mechanisms of action and resistance and adverse effects. In: UpToDate 4 August 2021., URL: https://www.uptodate.com/contents/beta-lactam-antibiotics-mechanisms-of-action-and-resistance-and-adverse-effects?search=cephalosporins&topicRef=480&source=see_link: (accessed 18 October 2022).
4. T Bui and C Preuss. 2022. Cephalosporins. [Updated 2022 Sep 21]. In: StatPearls [Internet]. In: URL: https://www.ncbi.nlm.nih.gov/books/NBK551517/ (accessed 1 November 2022).
5. Medsafe. 2020. *Datasheets and consumer medicine information* URL: https://www.medsafe.govt.nz/Medicines/infoSearch.asp (accessed 18 October 2022)
6. New Zealand Formulary (NZF). 2022. NZF v125: Antibacterial drugs 1 Nov 2022. URL:https://www.nzf.org.nz/nzf_2893, URL: https://www.nzf.org.nz/nzf_2893: (accessed 1 November 2022).
7. Te Whatu Ora Te Toka Tumai Auckland. 2022. Antimicrobial stewardship (AMS). URL:https://www.adhb.health.nz/health-professionals/resources/ams/#Guide (accessed 1 November 2022).
8. Best Practice Advisor centre (BPAC). 2017. Antbiotics choices for common infections 2017 edition. . URL:https://www.nzf.org.nz/nzf/resource/bpacnz-antibiotics-guide-2017.pdf (accessed 18 October 2022).
9. PHARMAC. 2022. *Hospital Medicines List: Ceftaroline fosmail* URL: https://schedule.pharmac.govt.nz/HMLOnline.php?edition=&osq=Ceftaroline+fosamil (accessed 18 November 2022).
10. Bora I, Demir AB and Uzun P. 2016. Nonconvulsive status epilepticus cases arising in connection with cephalosporins. *Epilepsy Behav Case Rep* 6: 23-7. DOI: 10.1016/j.ebcr.2016.04.005 (accessed 27 October 2022).
11. Grahl JJ, Stollings JL, Rakhit S, et al. 2018. Antimicrobial exposure and the risk of delirium in critically ill patients. *Crit Care* 22(1): 337. DOI: 10.1186/s13054-018-2262-z (accessed 19 November 2022).
12. Barbosa-Silva MC, Lima MN, Battaglini D, et al. 2021. Infectious disease-associated encephalopathies. *Crit Care* 25(1): 236. DOI: 10.1186/s13054-021-03659-6 (accessed 26 October 2022).
13. Triplett JD, Lawn ND, Chan J, et al. 2019. Cephalosporin-related neurotoxicity: Metabolic encephalopathy or non-convulsive status epilepticus? *J Clin Neurosci* 67: 163-166. DOI: 10.1016/j.jocn.2019.05.035 (accessed 26 October 2022).
14. Chalela J. 2022. Acute toxic-metabolic encephalopathy in adults. In: UpToDate 16 June 2020. URL:https://www.uptodate.com/contents/acute-toxic-metabolic-encephalopathy-in-adults (accessed 31 October 2022).
15. John Hopkins Medicine. 2022. *Types of seizures* URL: https://www.hopkinsmedicine.org/health/conditions-and-diseases/epilepsy/types-of-seizures (accessed 1 November 2022).
16. Martínez-Rodríguez JE, Barriga FJ, Santamaria J, et al. 2001. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. *Am J Med* 111(2): 115-9. DOI: 10.1016/s0002-9343(01)00767-7 (accessed 25 October 2022).
17. Al-Sadawi M, Rodriguez Ortega R, Sun N, et al. 2019. Jerky Movement with Ceftazidime: A Case of Ceftazidime-Induced Neurotoxicity with a Review of the Literature. *Case Rep Med* 2019: 8936478. DOI: 10.1155/2019/8936478 (accessed 26 October 2022).
18. Payne LE, Gagnon DJ, Riker RR, et al. 2017. Cefepime-induced neurotoxicity: a systematic review. *Crit Care* 21(1): 276. DOI: 10.1186/s13054-017-1856-1 (accessed 28 October 2022).

19. Treiman DM. 2001. GABAergic mechanisms in epilepsy. *Epilepsia* 42 Suppl 3: 8-12. DOI: 10.1046/j.1528-1157.2001.042suppl.3008.x (accessed 26 October 2022).
20. Wanleenuwat P, Suntharampillai N and Iwanowski P. 2020. Antibiotic-induced epileptic seizures: mechanisms of action and clinical considerations. *Seizure* 81: 167-174. DOI: 10.1016/j.seizure.2020.08.012 (accessed 20 October 2022).
21. Collins RD, Tverdek FP, Bruno JJ, et al. 2016. Probable Nonconvulsive Status Epilepticus With the Use of High-Dose Continuous Infusion Ceftazidime. *J Pharm Pract* 29(6): 564-568. DOI: 10.1177/0897190015608503 (accessed 1 November 2022).
22. Sugimoto M, Uchida I, Mashimo T, et al. 2003. Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. *Neuropharmacology* 45(3): 304-14. DOI: 10.1016/s0028-3908(03)00188-6 (accessed 2 November 2022).
23. Lacroix C, Kheloufi F, Montastruc F, et al. 2019. Serious central nervous system side effects of cephalosporins: A national analysis of serious reports registered in the French Pharmacovigilance Database. *J Neurol Sci* 398: 196-201. DOI: 10.1016/j.jns.2019.01.018 (accessed 17 November 2022).
24. New Zealand Formulary (NZF). 2022. NZF v125: Prescribing in renal impairment 1 November 2022 URL:https://nzf.org.nz/nzf_146: (accessed 7 November 2022).
25. Anto M, Iyer RS, Manuel A, et al. 2022. Ceftriaxone-induced encephalopathy in a patient with multicentric glioma. *Surg Neurol Int* 13: 303. DOI: 10.25259/sni_483_2022 (accessed 26 October 2022).
26. Zhao Y, Gan L, Ren L, et al. 2022. Factors influencing the blood-brain barrier permeability. *Brain Res* 1788: 147937. DOI: 10.1016/j.brainres.2022.147937 (accessed 1 November 2022).
27. Banks WA. 2009. Characteristics of compounds that cross the blood-brain barrier. *BMC neurology* 9 Suppl 1(Suppl 1): S3-S3. DOI: 10.1186/1471-2377-9-S1-S3 (accessed 27 October 2022).
28. Alahmari A. 2021. Blood-Brain Barrier Overview: Structural and Functional Correlation. *Neural plasticity* 2021: 6564585-6564585. DOI: 10.1155/2021/6564585 (accessed 14 November 2022).
29. Lutsar I and Friedland IR. 2000. Pharmacokinetics and Pharmacodynamics of Cephalosporins in Cerebrospinal Fluid. *Clinical Pharmacokinetics* 39(5): 335-343. DOI: 10.2165/00003088-200039050-00003 (accessed 21 October 2022).
30. Jadot L, Judong A, Canivet JL, et al. 2021. Ceftriaxone-induced Encephalopathy: A Pharmacokinetic Approach. *Eur J Case Rep Intern Med* 8(11): 003011. DOI: 10.12890/2021_003011 (accessed 28 October 2022).
31. Nau R, Sörgel F and Eiffert H. 2010. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev* 23(4): 858-83. DOI: 10.1128/cmr.00007-10 (accessed 1 November 2022).
32. Nishioka H, Cho Y, Irie K, et al. 2022. Ceftriaxone-associated encephalopathy in a patient with high levels of ceftriaxone in blood and cerebrospinal fluid. *Int J Infect Dis* 116: 223-225. DOI: 10.1016/j.ijid.2022.01.023 (accessed 26 October 2022).
33. Roncon-Albuquerque R, Jr., Pires I, Martins R, et al. 2009. Ceftriaxone-induced acute reversible encephalopathy in a patient treated for a urinary tract infection. *Neth J Med* 67(2): 72-5. (accessed 2 November 2022).
34. van Dam DG, Burgers DM, Foudraine N, et al. 2017. Treatment of cefuroxime-induced neurotoxicity with continuous venovenous haemofiltration. *Neth J Med* 75(1): 32-34. (accessed 1 November 2022).
35. Bhattacharyya S, Darby RR, Raibagkar P, et al. 2016. Antibiotic-associated encephalopathy. *Neurology* 86: 963 - 971. (accessed 28 October 2022).
36. Lacroix C, Bera-Jonville AP, Montastruc F, et al. 2021. Serious Neurological Adverse Events of Ceftriaxone. *Antibiotics (Basel)* 10(5): DOI: 10.3390/antibiotics10050540 (accessed 25 October 2022).
37. Gatti M, Raschi E and De Ponti F. 2021. Serious adverse events with novel beta-lactam/beta-lactamase inhibitor combinations: a large-scale pharmacovigilance analysis. *Eur J Clin Microbiol Infect Dis* 40(6): 1169-1176. DOI: 10.1007/s10096-020-04149-3 (accessed 31 October 2022).
38. Martin TCS, Chow S, Johns ST, et al. 2020. Ceftaroline-associated Encephalopathy in Patients With Severe Renal Impairment. *Clin Infect Dis* 70(9): 2002-2004. DOI: 10.1093/cid/ciz857 (accessed 27 October 2022).

39. Arkaravichien W, Tamungklang J and Arkaravichien T. 2006. Cefazolin induced seizures in hemodialysis patients. *J Med Assoc Thai* 89(11): 1981-3. (accessed 28 October 2022).
40. Bechtel TP, Slaughter RL and Moore TD. 1980. Seizures associated with high cerebrospinal fluid concentrations of cefazolin. *Am J Hosp Pharm* 37(2): 271-3. (accessed 31 October 2022).
41. Fernández-Torre JL, Paramio-Paz A, López-Delgado A, et al. 2018. De novo absence status epilepticus of late onset (DNASLO) precipitated by oral treatment with cefuroxime: description of an ambulatory case. *Epileptic Disord* 20(1): 73-76. DOI: 10.1684/epd.2017.0938 (accessed 1 November 2022).
42. Toda M, Yoshifuji A, Hosoya K, et al. 2022. Ceftazidime encephalopathy developed without the elevation of cerebrospinal fluid concentration of ceftazidime: A case report of two cases. *J Infect Chemother* 28(12): 1667-1671. DOI: 10.1016/j.jiac.2022.08.011 (accessed 1 November 2022).
43. Pingue V, Penati R, Nardone A, et al. 2020. Ceftazidime/avibactam neurotoxicity in an adult patient with normal renal function. *Clin Microbiol Infect*, DOI:10.1016/j.cmi.2020.11.031: DOI: 10.1016/j.cmi.2020.11.031 (accessed 28 October 2022).
44. Futagi Y, Ito Y, Nakade J, et al. 2022. Ceftriaxone-induced encephalopathy in a patient with a solitary kidney. *Int J Infect Dis* 122: 722-724. DOI: 10.1016/j.ijid.2022.07.036 (accessed 1 November 2022).
45. Onogi C, Osada A, Imai K, et al. 2022. Two cases of ceftriaxone-induced encephalopathy treated by hemoperfusion in hemodialysis patients. *Hemodial Int* 26(3): E27-e30. DOI: 10.1111/hdi.13018 (accessed 1 November 2022).
46. Food and Drug Administration (FDA). 2012. *FDA Drug Safety Communication: Cefepime and risk of seizures in patients not receiving dosage adjustments for kidney impairment* URL: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-cefepime-and-risk-seizure-patients-not-receiving-dosage-adjustments (accessed 3 November 2022).
47. PRAC. 2020. *PRAC recommendations on signals: adopted at the 26-29 October PRAC meeting.* URL: https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-26-29-october-2020-prac-meeting_en.pdf (accessed 1 November 2022).
48. Health Canada. 2021. *Summary Safety Review - Ceftriaxone-containing products-Health Canada* URL: https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00257 (accessed 2 November 2022).
49. Health Canada. 2022. *New safety and effectivess reviews* URL: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/new.html (accessed 18 October 2022).
50. Therapeutic Goods Administration (TGA). 2021. *Ceftriaxone and risk of hepatitis and encephalopathy* URL: https://www.tga.gov.au/news/safety-updates/ceftriaxone-and-risk-hepatitis-and-encephalopathy (accessed 1 Novemeber 2022).