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Risk of neurotoxicity with cephalosporins

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Key messages

- There have been reports of neurotoxicity with cephalosporins, including encephalopathy, seizures and/or myoclonus.
- Risk factors include older age groups, renal impairment, underlying central nervous system disorders and intravenous administration.
- Consider cephalosporins as a potential cause of neurotoxicity in patients with these risk factors and an unexplained, new onset neurological condition.

The topic of cephalosporins and neurotoxicity was recently discussed at the December 2022 Medicines Adverse Reaction Committee (MARC) meeting.

The MARC considered the risk of neurotoxicity with cephalosporins to be a class effect.

Medsafe is working with the sponsors of cephalosporin products to update the data sheets as per the MARC's recommendations (see MARC's remarks in this edition of *Prescriber Update*).

Neurotoxicity may occur with all cephalosporins

Cephalosporins are broad-spectrum beta-lactam antibiotics used in primary and secondary care to treat a range of infections.[1]

Cephalosporins are grouped into 5 generations based on their antibacterial properties and their discovery.[2] Table 1 outlines the cephalosporins generally available in New Zealand, by generation.

Table 1: Cephalosporins available in New Zealand, by generation

1st generation	2nd generation	3rd generation	4th generation	5th generation

Cefazolin Cefalexin	Cefuroxime Cefaclor	Cefotaxime Ceftazidime Ceftriaxone	Cefepime	Ceftaroline fosamil Ceftolozane*

* Ceftolozane is available in combination with tazobactam.

Source: Medsafe. *Data sheets and Consumer Medicine Information*. URL: medsafe.govt.nz/Medicines/infoSearch.asp (accessed 9 January 2023).

Case report and case series reviews found that compared with other cephalosporins, cefepime was associated with the most reports of neurotoxicity internationally.[3,4] However, neurotoxicity has been reported with all generations of cephalosporins.[3,4]

Cephalosporin-induced neurotoxicity may present as a range of conditions

Reports of neurotoxicity with cephalosporins are mainly characterised by encephalopathy, myoclonus and/or seizures.[3,5]

Encephalopathy is a broad term which refers to brain dysfunction. It describes an altered mental state, representing a spectrum of symptoms from confusion to depressed levels of consciousness.[6]

Seizures associated with cephalosporins may present as either convulsive or non-convulsive.[7] A disruption in the neurotransmitter gamma-aminobutyric acid (GABA) function is proposed to be a possible mechanism for such events.[8]

Symptoms of neurotoxicity have been reported to develop within several days after starting treatment and to resolve following discontinuation.[3,7]

Renal impairment is a risk factor, especially if doses are not adjusted

Cephalosporins are excreted by the kidneys. In patients with renal impairment, accumulation can occur, especially when doses are not adjusted appropriately, potentially leading to toxic effects.[3,7]

Additional risk factors for cephalosporin-induced neurotoxicity include older age groups, underlying central nervous system (CNS) disorders and high doses of cephalosporins administered by intravenous injection.[3,7]

Critically unwell patients may experience increased penetration of cephalosporins into the CNS due to blood-brain barrier disruption, which may increase their susceptibility to neurotoxicity.[6,8]

Advice for health professionals

Recognition of cephalosporin-induced neurotoxicity may be challenging. Patients receiving antibiotics often have multiple potential causes of neurological conditions.[6,8]

At the December 2022 meeting, the MARC recommended that health professionals should consider cephalosporin-induced neurotoxicity in patients with the above risk factors and an unexplained, new onset neurological condition.[9] In such cases, withdrawal of the medicine may be appropriate.[9]

New Zealand case reports

As of 31 October 2022, the Centre for Adverse Reactions Monitoring (CARM) had received several reports that potentially describe cephalosporin-induced neurotoxicity, as shown in Table 2.

Adverse reactions reported in these cases included seizure, convulsion, myoclonus, confusion, encephalopathy, agitation, hallucination and delirium.

Table 2: Potential cases of cephalosporin-induced neurotoxicity reported to the Centre for Adverse Reactions Monitoring (CARM), by generation and cephalosporin, as of 31 October 2022

Generation[a]	Cephalosporin	No. of reports	CARM IDs
1st	Cefazolin	7	58339, 77512, 86695, 97392, 105241, 122558, 137985
	Cefalexin	2	123136, 136282
2nd	Cefuroxime	6	24559, 26025, 26764[b], 52754, 57256, 87469
	Cefaclor	3	22512, 33509, 50548
3rd	Cefotaxime	2	26764,[b] 105295
	Ceftazidime	2	28172, 136000
	Ceftriaxone	2	107950, 110187
4th	Cefepime	2	98398, 108616

Notes:

a. There were no reports for the 5th generation cephalosporins ceftaroline and ceftolozane.

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

Source: Centre for Adverse Reactions Monitoring

More information

See the sponsors' data sheets and Consumer Medicine Information (CMI) published on the Medsafe website.

- Search for a cephalosporin data sheet or CMI

References

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