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Contents

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MINISTRY OF HEALTH

Risk of neurotoxicity with cephalosporins

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' on page 10 of 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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Kambô – leave it with frogs

Key messages

- The frog species *Phyllomedusa bicolor* produces a poisonous secretion as a defence mechanism.
- In traditional Kambô rituals, this poisonous secretion is applied transdermally.
- Serious and life-threatening side effects have been reported following application of this poisonous secretion.

A case has been reported to the Centre for Adverse Reactions Monitoring (CARM) where the individual developed hypersensitivity vasculitis in relation to a Kambô ritual.

What is Kambô?

Kambô is a purifying ritual, which has a long history of use in South American traditional medicine. In the traditional Kambô ritual, a shaman uses a hot stick to create a series of small burns in the individual's skin, and then applies a secretion from the frog species *Phyllomedusa bicolor* to the fresh wound.[1,2]

P. bicolor, also named the giant leaf frog, is widely distributed in the rainforests of the Amazon basin, including in Brazil, Colombia and Bolivia.[1-3] The frog can be more than 10 centimetres long and is green with a white belly (Figure 1).[1,3]

As a defence mechanism, the frog produces a skin secretion that contains many different substances, such as alkaloids, peptides and proteins. The frog must be stressed to produce the secretion. For the traditional Kambô ritual, this is

accomplished in different ways, such as tying the captured frog up and poking it. The secretion is then scraped from its skin and the frog is released.[1,3]

Figure 1: Image of the frog species *Phyllomedusa bicolor*

Source: Silva FVAD, Monteiro WM and Bernarde PS. 2019. 'Kambô' frog (Phyllomedusa bicolor): Use in folk medicine and potential health risks. *Revista da Sociedade Brasileira de Medicina Tropical* 52: e20180467. DOI: 10.1590/0037-8682-0467-2018. Note that the original has been modified: only image A is shown; images B, C and D are not. Creative Commons Attribution 4.0 International License.

No clinical evidence to support therapeutic claims

The Kambô ritual was originally performed by shamans in South American as a purification ritual for the indigenous tribes. Over time, some aspects of the ritual have been appropriated and used in countries throughout the world. With this spread, the reported reasons for use have increased and include claims of therapeutic benefits and healing properties.[1-4]

These claims have been made without supporting clinical evidence. No beneficial effects of the frog secretion have been scientifically tested or demonstrated in the literature.[1,2]

Side effects

Serious and life-threatening side effects have been reported following application of the frog secretion.[1-5]

A physiological reaction is induced within minutes of application, with effects such as tachycardia, intense vomiting and sweating. These effects generally subside in about an hour, followed by a state of apathy and drowsiness.[1]

The secretion contains a variety of peptides and other substances with intense pharmacological actions, including the opioid peptides deltorphin and dermorphin, as well as peptides with antimicrobial, gastrointestinal and cardiovascular effects.[1,4]

It has been suggested that most side effects of the secretion may be associated with the CNS depressant and cardiovascular effects of its peptides. Additionally, many side effects are thought to be dose dependent.[1]

Other side effects have been described in the literature. A published case report describes a 33-year-old female with a history of periodic use of frog secretion in Kambô rituals, who presented with asthenia, malaise and myalgia, and was diagnosed with dermatomyositis.[5]

A recent literature review of acute poisoning after application of frog secretions from *Phyllomedusa bicolor* reported numerous symptoms including vomiting, diarrhoea, epilepsy, muscle disorders, mood disturbances and hydroelectrolytic imbalance. Various Kambô-associated pathologies were also described, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), acute renal failure, dermatomyositis, rupture of oesophagus, severe psychosis, toxic hepatitis and death.[4]

Hyponatraemia may be associated with Kambô due to the development of SIADH and the common practice of ingesting large volumes of water as part of these rituals.[4]

Regulation

The frog secretion used in Kambô rituals is not an approved medicine in New Zealand, and therefore its safety, quality or effectiveness has not been assessed.

References

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Quarterly summary of recent safety communications

The table below is a summary of recent safety communications to health care professionals and consumers, published on the Medsafe website.

Date	Communication	Topic
28/11/2022	Monitoring	Possible risk of seizures with clonidine
22/11/2022	Monitoring	Goserelin (Teva) 3.6mg and 10.8 mg implants and reports of issues when administering this medicine
07/11/2022	Dear Healthcare Professional Letter	Setrona - Supply of Australian-labelled Setrona 100mg tablets in New Zealand (PDF, 2 pages, 415KB)

Starting empagliflozin or dapagliflozin in patients on lithium? Monitor lithium levels

Key messages

- Sodium-glucose co-transporter 2 (SGLT2) inhibitors, such as empagliflozin and dapagliflozin, may increase the renal excretion of lithium and lead to decreased serum lithium levels.
- Monitor the patient's serum lithium levels more frequently when a SGLT2 inhibitor is initiated or following dose changes. Adjust the lithium dose if necessary.

Medsafe has requested data sheet updates for sodium-glucose co-transporter 2 (SGLT2) inhibitors (empagliflozin and dapagliflozin) and lithium products to include information on the drug-drug interaction between these medicines.

Inhibition of SGLT2 may enhance the renal excretion of lithium

The sodium-glucose co-transporter 2 is responsible for the reabsorption of glucose and sodium in the renal tubules.[1,2]

SGLT2 inhibitors are used in the treatment of type 2 diabetes mellitus to improve glycaemic control. They promote glucose excretion by reducing renal absorption of glucose into the blood stream.[1,2]

Lithium can substitute for sodium, presumably because it is atomically similar to sodium, and use sodium-transporting systems.[3] Therefore, concomitant use of SGLT2 inhibitors and lithium may increase the renal excretion of lithium and lead to decreased serum lithium levels.[1,2,4]

Routine monitoring of serum lithium levels is important to ensure they are within therapeutic range

Lithium has a narrow therapeutic index. Routine and regular monitoring is required to ensure appropriate dosing.[5]

Many medicines can influence lithium clearance, by altering renal blood flow, glomerular filtration rate and sodium balance.[3]

Monitor the patient's serum lithium levels more frequently when a SGLT2 inhibitor is initiated or following dose changes. Adjust the dose of lithium if necessary.[1,2]

New Zealand case reports

Up to 9 January 2023, the Centre for Adverse Reactions Monitoring (CARM) had not received any reports of an interaction between lithium and SGLT2 inhibitors (empagliflozin, dapagliflozin).

More information

Medsafe: Drug interactions with lithium and therapeutic drug monitoring

References

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2. Boehringer Ingelheim (N.Z.) Limited. 2022. *Jardiance New Zealand Data Sheet* 29 August 2022. URL: medsafe.govt.nz/profs/Datasheet/j/jardiancetab.pdf (accessed 12 January 2023).
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Metoclopramide: risk of dystonic side effects in children and young adults

Key messages

- Metoclopramide is indicated for treatment of nausea and vomiting.
- Due to the risk of dystonic side effects, metoclopramide use in children and young adults (aged 1 to 19 years, inclusive) is limited to certain conditions and for second-line therapy.
- Dystonia can occur after a single dose of metoclopramide and occurs more frequently in children and young adults, and in females.
- Do not use in people under 20 years of age unless absolutely necessary, and then strictly follow the dose recommendations in the metoclopramide data sheets to reduce the risk of dystonic side effects.

The Centre for Adverse Reactions Monitoring (CARM) has received several reports recently of dystonic reactions in children prescribed metoclopramide. This article is a reminder that due to the risk of dystonic side effects, metoclopramide use in children and young adults is limited to certain conditions and for second-line therapy.

Metoclopramide

Metoclopramide is an antiemetic medicine indicated for the treatment of nausea and vomiting and digestive disorders.[1-3] Metoclopramide is a dopamine receptor antagonist.[4] It is classified as a cholinomimetic because it increases the transmission of acetylcholine at muscarinic receptors.[5]

In New Zealand, metoclopramide is available as tablets and as a solution for injection.[1,6]

Metoclopramide can cause dystonic side effects, which occur in approximately 1% of patients.[1] Dystonia can occur following a single dose of metoclopramide and occurs more frequently in children and young adults.[1]

Conditions

Due to the risk of dystonic side effects, metoclopramide use in children and young adults (aged 1 to 19 years, inclusive) is limited to certain conditions and as second-line therapy,[1,6] as shown in Table 1. Note that the tablets are only indicated for young adults aged 15 to 19 years.

Table 1: Metoclopramide – conditions for use in children and young adults, by dose form

Dose form	Age	Conditions
Solution for injection[a,b]	1 to 19 years (inclusive)	Second-line therapy for: • severe intractable vomiting of known cause • vomiting associated with radiation therapy or intolerance to cytotoxic drugs • assisting in small bowel intubation

Tablet[c]	15 to 19 years (inclusive)	Second-line therapy for: • severe intractable vomiting of known cause • vomiting associated with radiation therapy and intolerance to cytotoxic medicines • aiding gastrointestinal intubation • premedication before surgical procedures

Notes:

a. Pfizer New Zealand Limited. 2021. *Metoclopramide Injection New Zealand Data Sheet* 9 July 2021. URL: medsafe.govt.nz/profs/Datasheet/m/Metoclopramidepfizerinj.pdf (accessed 17 January 2023).

b. Baxter Healthcare Ltd. 2019. *Metoclopramide-Baxter New Zealand Data Sheet* 7 November 2019. URL: medsafe.govt.nz/profs/Datasheet/m/MetoclopramideClarisinj.pdf (accessed 17 January 2023).

c. Teva Pharma (New Zealand) Limited. 2017. *Metoclopramide Actavis New Zealand Data Sheet* 22 May 2017. URL: medsafe.govt.nz/profs/Datasheet/m/MetoclopramideActavistab.pdf (accessed 17 January 2023).

Dystonia

Dystonia is a movement disorder. It involves uncontrolled muscle contractions, which can cause abnormal body movements such as repetitive movements or parts of the body twisting in unusual ways.[7,8] Dystonic movements also typically have a pattern and may be continuous or intermittent.[7] Dystonia can affect a person's whole body or one part of the body.[8]

Dystonic side effects are the most common type of extrapyramidal side effects associated with the use of metoclopramide.[4,5] As well as occurring more frequently in children and young adults, dystonic side effects associated with the use of metoclopramide have been reported as occurring more frequently in females than males and with higher doses.[4]

To reduce the risk of dystonic side effects, strictly follow the dose recommendations in the data sheets.[1,6]

New Zealand case reports

As of 1 December 2022, the Centre for Adverse Reactions Monitoring had 372 reports relating to metoclopramide. Of these, 23% (86 reports) were in patients aged 19 years and under.

Most of the 372 metoclopramide reports involved females (77%). Of the 86 reports in patients aged 19 years and under, 83% were in females.

Dystonia was the most frequently reported adverse reaction associated with metoclopramide. Table 2 shows the top 5 reactions reported for metoclopramide in children and young adults (aged 19 years and under).

Table 2: Top 5 reactions reported for metoclopramide in children and young adults (≤19 years), as of 1 December 2022

Adverse drug reaction	Number of reports
Dystonia	44
Oculogyric crisis	14
Extrapyramidal disorder	8
Anxiety	5
Trismus	4

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 data sheet or CMI

References

1. Teva Pharma (New Zealand) Limited. 2017. *Metoclopramide Actavis New Zealand Data Sheet* 22 May 2017. URL: medsafe.govt.nz/profs/Datasheet/m/MetoclopramideActavistab.pdf (accessed 16 January 2023).
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MARC's remarks: December 2022 meeting

The Medicines Adverse Reactions Committee (MARC) convened on 1 December 2022.

The Committee reviewed the risk of neurotoxicity with **cephalosporin antibiotics**. Although the available data is limited, the Committee considered an association between neurotoxicity and the cephalosporin class cannot be discounted. They agreed that recognition of neurotoxicity in patients taking cephalosporins may be challenging. The Committee recommended that all cephalosporin data sheets should include consistent messaging on the risk of neurotoxicity. See 'Risk of neurotoxicity with cephalosporins' on page 2 of this edition of *Prescriber Update*.

The safety of **pregabalin** when taken during pregnancy was discussed. European prescribing information has been updated to include the results of a Nordic observational study that suggested that the risk of major congenital malformations (MCM) among children exposed to pregabalin in the first trimester of pregnancy was slightly higher compared to unexposed children. However, this association was no longer statistically significant after adjusting for confounding factors.[1]

The Committee noted that the current pregabalin data sheet includes a strong warning that use in the first trimester of pregnancy may cause major birth defects in the unborn child and that pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. The Committee considered that the study results did not change or strengthen this warning, and there was no need to update the data sheet information on use in pregnancy at this time. The Committee recommended that the safety of pregabalin in pregnancy should continue to be monitored and reviewed again as new information becomes available.

See the Medsafe website for the MARC meeting minutes and the reports presented to the MARC.

Reference

1. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP). 2020. *A Population based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes - final study report* 1 June 2020. URL: encepp.eu/encepp/viewResource.htm?id=36881 (accessed 16 September 2022).

Digoxin toxicity – don't break my heart

Key messages

- Digoxin is a cardiac glycoside used in the management of systolic heart failure and certain supraventricular arrhythmias.
- Digoxin has a narrow therapeutic index, and digoxin toxicity can occur when serum levels are within the therapeutic range. Toxicity can occur following an acute overdose and in patients on long-term therapy.
- Patients with digoxin toxicity may present with cardiac and non-cardiac symptoms.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of digoxin toxicity, where the patient experienced renal failure, hyperkalaemia, bradycardia and cardiac failure (CARM ID: 144388). Although this patient experienced severe cardiac problems, the clinical features of digoxin toxicity can be non-specific and are discussed further in this article.

Digoxin therapy

Digoxin is a cardiac glycoside that increases the force of myocardial contraction and reduces conductivity within the atrioventricular node of the heart. It is used in the management of systolic heart failure and certain supraventricular arrhythmias, particularly atrial flutter and fibrillation.[1]

The dose of digoxin should be tailored on an individual basis. Factors to consider include:

- indication for digoxin therapy[1]
- patient age[1]
- lean body weight[1]
- renal function.[1]

Digoxin is initiated via a rapid or slow loading dose, followed by a maintenance dose that ranges from 62.5 mcg to 250 mcg per day in adults and children over 10 years of age.[1,2] In order to reduce the risk of medication errors, it is important that healthcare professionals counsel patients about dose changes.

Digoxin toxicity

Digoxin has a narrow therapeutic index, and toxicity is a well-recognised clinical problem associated with significant morbidity and mortality. Toxicity can occur following an acute overdose and in patients on long-term therapy.[3]

The clinical features of toxicity are often non-specific, and patients can present with visual disturbances and cardiac (dysrhythmia), gastrointestinal (nausea, vomiting, abdominal pain) and neurological (confusion, weakness, delirium) symptoms.[3]

Serum digoxin levels can be used to assist diagnosis, but they do not correlate consistently with the clinical manifestations of toxicity.[3] Patients are at an increased risk of digoxin toxicity when serum digoxin levels rise above 2.6 nmol/L (2 ng/mL).[3,4] However, toxicity can also occur when serum levels are within the therapeutic range, especially in the presence of certain electrolyte disturbances (eg, hypokalaemia).[3,4]

There are several risk factors for digoxin toxicity, and serum digoxin levels should be interpreted in conjunction with other clinical markers, such as serum potassium levels and renal and thyroid function tests.[5]

Risk factors for digoxin toxicity (list not exhaustive)

- **Renal impairment**: digoxin is eliminated in the urine; the half-life of digoxin is prolonged in patients with kidney disease.[2]
- **Concomitant medicines**: there are a number of important drug interactions with digoxin, including inducers/inhibitors of P-glycoprotein and medicines associated with electrolyte abnormalities (eg, diuretics).[2]
- **Age**: the incidence of digoxin toxicity increases with age.[6]
- **Comorbidities**: an increase in the number of comorbid conditions, including amyloidosis, thyroid disease and cardiovascular disease, may increase patient susceptibility to digoxin toxicity.[6]
- **Electrolyte imbalances**: several electrolyte abnormalities, including hypokalaemia, hypomagnesemia and hypercalcemia, increase patient susceptibility to the toxic effects of digoxin.[3]
- **Acute illnesses** that may cause dehydration or acute renal insufficiency.[3]

Management of toxicity includes standard supportive care, correction of electrolyte imbalances, activated charcoal, atropine for acute bradyarrhythmias, and administration of an antidote.[1,7]

Contact the National Poisons Centre and/or access TOXINZ for advice on the management of digoxin overdose.

CARM reports

Between January 2008 to December 2022, CARM received 88 case reports with symptoms suggestive of digoxin toxicity, including 5 where drug toxicity was reported as an adverse reaction (CARM ID numbers: 81719, 111281, 113571, 141350, 144388).

Conclusion

Due to digoxin's narrow therapeutic index, healthcare professionals should remain vigilant about the possibility of digoxin toxicity and consider dose adjustments in patients predisposed to toxicity. Given the potential for harm and the non-specific symptoms of toxicity, remind patients taking digoxin to seek medical attention if they feel unwell.

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Use caution if switching between long-acting methylphenidate products due to formulation differences

Key messages

- Different long-acting methylphenidate products have different formulations, with distinct release profiles and dosing requirements, which may affect symptom management.
- The choice of long-acting methylphenidate product should match the patient's needs.
- Use caution if switching between long-acting methylphenidate products (brands) and communicate any changes to the patient.

The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom recently published advice for healthcare professionals to use caution if switching patients between long-acting methylphenidate products.[1] This article provides similar advice for New Zealand prescribers.

Methylphenidate

Methylphenidate is a central nervous system stimulant used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).[2] There are products with immediate-release and long-acting formulations available in New Zealand. Long-acting formulations are usually labelled as extended release, modified release, long acting (LA) or sustained release (SR).

The long-acting methylphenidate products available in New Zealand are Concerta, Methylphenidate Extended Release (Teva), Ritalin LA and Rubifen SR.

Formulation differences between long-acting methylphenidate products

Because the long-acting methylphenidate products are formulated differently, there is a need for caution when switching patients between products (brands).

Methylphenidate in long-acting formulations is released in two stages, due to the immediate-release and modified-release components.[1] Following oral administration, there is a rapid increase in plasma concentration reaching an initial maximum at about 1-2 hours. The plasma concentration then continues to increase more gradually until peak plasma concentration (C_{max}) is reached at about 6-8 hours.[2, 3-5] The biphasic release profiles of different long-acting methylphenidate products may not be comparable due to formulation differences in the ratio of immediate release and modified release components.[1]

Long-acting methylphenidate products may also differ in other ways, including the dose strengths available, mechanism of release, pharmacokinetics, plasma concentration-time profiles, bioavailability and whether the medicine is taken with or without food.[1]

In addition, at the individual patient level, there is significant variability in the pharmacokinetic profiles of long-acting methylphenidate products throughout the day.[6] Therefore, the patient's response to any product or dosing regimen may vary substantially.[6]

Together, these differences may contribute to a change in clinical effect when long-acting products are used interchangeably. The same dose of different products may not necessarily be equivalent in terms of the clinical effect.

Communicate product (brand) changes to the patient, including reasons for the change, how to use the new medicine, possible changes they may experience in symptom management and potential side effects (and what to do if these occur).[1] Frequent switching between methylphenidate products is not recommended.[1]

More information

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

- Search for a methylphenidate data sheet or CMI

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Recent approvals: new active ingredients or new indications

For the period 16 October 2022 to 15 January 2023.

Recent approvals of medicines with new active ingredients

Trade name (active ingredient)	Dose form and strength(s)	Therapeutic area
Luxturna (voretigene neparvovec)	Concentrate for injection: 5x10^12 VP/mL	Inherited retinal dystrophy caused by pathological biallelic RPE65 mutations

Approved medicines with new indications

Trade Name (active ingredient)	Dose form and strength(s)	New therapeutic area(s)
Nucala (mepolizumab)	Powder for injection: 100 mg/mL Solution for injection (pre-filled pen and pre-filled syringe): 100 mg/mL	Chronic rhinosinusitis with nasal polyps Hypereosinophilic syndrome

See the Medsafe website for:

- more information about these medicines
- data sheets of currently marketed medicines.

Administration of methotrexate in patients taking sodium valproate may reduce seizure or mood control

Key messages

- Some case reports describe a significant reduction in the serum level of sodium valproate soon after administration of methotrexate, resulting in seizures.
- Competitive protein binding, displacement from albumin and rapid metabolism are possible causes of the reduction in serum sodium valproate levels.
- When starting methotrexate therapy in valproate patients, monitor the patient's clinical response (seizure control or mood control) and serum valproate levels as appropriate.

Background

The sodium valproate (Epilim) data sheet has been updated to include an interaction with methotrexate. Some case reports describe a significant reduction in the serum level of sodium valproate after administration of methotrexate, resulting in seizures.[1]

This article highlights the published case reports, plus the possible mechanism for this drug-drug interaction and its management.

Case reports

Two case reports in the literature have documented this drug-drug interaction. The first case involved the use of low-dose weekly methotrexate for the treatment of psoriasis[2] while the second case involved the use of high-dose methotrexate infusion for childhood leukaemia.[3] In both cases, significant reductions in serum sodium valproate levels were observed soon after administration of methotrexate, resulting in seizures.[2,3]

As of 1 December 2022, no cases of this drug-drug interaction had been reported to the Centre for Adverse Reactions Monitoring.

Proposed mechanism for the interaction

Methotrexate (a weak acid and 75% bound to albumin) competes with sodium valproate (90% bound to albumin) for binding to albumin. Following the displacement of sodium valproate from albumin, a larger unbound proportion is available for metabolism by the liver, resulting in decreased serum sodium valproate levels.[2]

Management of the interaction

Where concurrent use of sodium valproate and methotrexate is indicated, healthcare professionals should be aware of the potential for reduction in seizure or mood control.[1]

Monitor the patient's clinical response from sodium valproate treatment and consider monitoring serum sodium valproate levels as appropriate.[1]

Management of this interaction may require dose adjustment of sodium valproate. If clinically appropriate, a non-interacting alternative to methotrexate should be considered in patients taking sodium valproate.[2]

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We need your help!

M² MEDICINES MONITORING

Please send your reports to CARM for the potential safety issues* listed in the table below.

Medicine(s)	Potential safety issue	Active monitoring ends
Clonidine	Seizures	28 May 2023

- M² (Medicines Monitoring) is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Please send your report to CARM (as for any suspected adverse reaction). This can be done even if the reaction happened some time ago. Please include as much information as possible as this helps the medical assessors at CARM to investigate whether the medicine caused the reaction.
- For further information about M², see the Medsafe website.

* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

Gathering knowledge from adverse reaction reports: March 2023

Adverse reaction reporting is an important component of medicine safety monitoring. Case reports can highlight significant safety issues concerning therapeutic products and their use.

The table below presents a selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 145403 **Age**: 50 **Gender**: Female **Medicine(s)**: Bupropion + naltrexone **Reaction(s)**: Amnesia, headache	The patient experienced a type of blackout, during which she was fully functional but had no recollection of events. She went to bed and had a headache upon wakening.
	Amnesia is listed as an uncommon adverse drug reaction in the **Contrave** data sheet. Headaches are also listed.
CARM ID: 144608 **Age**: 66 **Gender**: Male **Medicine(s)**: Ivermectin **Reaction(s)**: Generalised tonic-clonic seizure	A patient with COVID-19 self-medicated with ivermectin and had tonic-clonic seizures.
	Ivermectin is not indicated for treatment of COVID-19. Seizures are listed as a very rare postmarketing ADR in the **Stromectol** data sheet.
CARM ID: 145103 **Age:** 67 **Gender:** Male **Medicine(s):** Atenolol **Reaction(s):** Hallucination, confusional state	After starting atenolol, the patient experienced command hallucinations that led them to act erratically and put their life in danger.
	Hallucinations and psychoses are listed in the **Atenolol Viatris** data sheet.
CARM ID: 145181 **Age**: 24 **Gender**: Female **Medicine(s)**: Venlafaxine, rizatriptan **Reaction(s)**: Serotonin syndrome, drug interaction	A patient on venlafaxine was prescribed rizatriptan. She experienced palpitations, sinus tachycardia and clonus and was diagnosed with serotonin syndrome.
	Rizatriptan (a triptan) and venlafaxine (a serotonin norepinephrine reuptake inhibitor; SNRI) are serotonergic medicines. The **Rizamelt** and **Enlafax** data sheets contain warnings for serotonin syndrome associated with concomitant use of triptans with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). These reactions can be life-threatening and involve altered mental status, autonomic instability and neuromuscular abnormalities.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 145293 **Age**: 25 **Gender**: Female **Medicine(s)**: Azithromycin **Reaction(s)**: Tongue discolouration	The patient's tongue turned yellow after taking azithromycin.
	Tongue discolouration is listed in the **Apo-azithromycin** and **Zithromax** data sheets.

Notes:

a. Only the medicines suspected to have caused the reaction are listed in the table.

b. The reactions listed in the 'Case details' column are coded according to the Medical Dictionary for Regulatory Activities (MedDRA), an internationally used set of standardised terms relating to medical conditions, medicines and medical devices. The reactions listed in the 'Reaction description' column are based on what was reported to CARM, and do not always match the MedDRA term.

c. If the suspect medicine's brand name is not described in the report to CARM, only the data sheet for the funded medicine is included in the table.

Information about suspected adverse reactions reported to CARM is available on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS).

By selecting the ingredient of a medicine, you can find out:

- the number of reports and suspected adverse reactions for that ingredient. The suspected reactions are grouped by body system or organs (Summary report)
- single case reports, listing the medicines involved that contain the ingredient and the suspected adverse reactions (Detail report).

Role of dihydropyrimidine dehydrogenase deficiency in systemic fluoropyrimidine-related toxicity

Key messages

- Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme responsible for the breakdown of fluoropyrimidines (eg, fluorouracil and capecitabine) in the body.
- The activity of this enzyme varies widely, most often due to polymorphisms in the *DPYD* gene.
- Individuals with partial or complete DPD deficiency treated with fluoropyrimidines have an increased risk of severe or fatal toxicities. Toxicity usually occurs during the first treatment cycle or after a dose increase.
- In some countries, DPD status can be investigated using genotype and/or phenotype methods, although the optimal screening method has not been established. Routine screening of DPD status is not available in New Zealand.

Background

The Centre for Adverse Reactions Monitoring (CARM) recently received 2 fatal case reports involving systemic fluoropyrimidines (fluorouracil and capecitabine; CARM IDs 140395 and 143421, respectively). Suspected dihydropyrimidine dehydrogenase (DPD) deficiency was thought to contribute to severe fluoropyrimidine toxicity in both cases.

This article highlights the role of DPD in fluoropyrimidine metabolism, the genetic basis of DPD deficiency and treatment considerations for DPD-deficient patients receiving fluoropyrimidines.

What are fluoropyrimidines?

Fluorouracil and capecitabine are fluoropyrimidines used to treat a wide variety of cancers. Fluorouracil is a pyrimidine analogue antimetabolite that interferes with DNA and RNA synthesis[1], while capecitabine is a prodrug of fluorouracil.[2]

The *DPYD* gene encodes DPD and is highly polymorphic

DPD is the rate-limiting enzyme responsible for inactivating fluorouracil in the body. The activity of this enzyme can vary from a partial to a complete loss of activity among DPD-deficient individuals.[3]

DPD deficiency is most often the result of genetic polymorphism in the *DPYD* gene that encodes DPD. *DPYD* is highly polymorphic, with more than 160 genetic variants identified to date, some resulting in altered or near-complete loss of enzyme activity.[4] DPYD*2A is the most well-known *DPYD* variant associated with DPD deficiency.[5] Variants DPYD*13, c.2846A>T and HapB3 have also been associated with altered DPD activity.[5]

In the European population, the prevalence of partial and complete DPD deficiency is approximately 3–9% and 0.01–0.5%, respectively.[4] There is limited data on the prevalence of DPD deficiency in other ethnic groups. However, it has been suggested that Asian and African populations are at greater risk of DPD deficiency.[4]

Treatment considerations in DPD-deficient patients

Patients with partial or complete DPD deficiency treated with a standard dose of a fluoropyrimidine will have increased levels of active metabolites. These individuals

have an increased risk of severe or even fatal fluoropyrimidine-related toxicities such as diarrhoea, mucositis, myelosuppression and neurotoxicity.[5]

Toxicity in DPD-deficient patients usually occurs during the first treatment cycle or after a dose increase.[2,6] These reactions tend to occur earlier and be more severe and prolonged compared to typical fluoropyrimidine toxicity.[5]

Consider the following if the patient's DPD status is known.

- In patients with a known **complete loss** of DPD activity: there is no safe dose of fluorouracil and capecitabine. Treatment is contraindicated in these patients.[2,6]
- In patients with a known **partial** DPD deficiency: initiate treatment with fluoropyrimidines with extreme caution. A reduced starting dose, frequent monitoring, and subsequent dose adjustments may be required – consult local guidelines. The clinical efficacy of fluoropyrimidines with reduced doses remains uncertain.[2,6]

Other risk factors for developing fluoropyrimidine-related toxicity

The following factors may increase an individual's risk of fluoropyrimidine-related toxicity:

- renal impairment – the incidence of severe to life-threatening toxicity is higher in patients with renal impairment[7]
- drug-drug interactions – through pharmacokinetic interactions or the additive effects of other myelosuppressive medicines[6]
- female sex[6]
- patients aged 70 years or older.[6]

Investigating individual DPD status

In some countries, DPD status may be investigated by DPYD genotyping and measuring the DPD phenotype (uracil levels).[4,7] Currently, there are uncertainties regarding the optimal method for determining an individual's risk of fluoropyrimidine-related toxicity.[4]

The fluorouracil and capecitabine data sheets recommend that DPD status of the patient is determined before therapy through laboratory testing for the detection of complete or partial DPD deficiency, *where testing is available*.[2,6] Determining DPD status can also be useful when evaluating patients experiencing fluoropyrimidine-related toxicities.[2,6]

At present, DPD testing (either genotype or phenotype testing) is not routinely available in New Zealand. However, there is ongoing clinical and translational research in this area, including which tests would be clinically relevant for the New Zealand population.

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