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Department of Health and Ageing  
Therapeutic Goods Administration

# Medicines Safety Update

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## Vancomycin and nephrotoxicity

Health professionals are reminded of the risk of nephrotoxicity associated with intravenous infusion of vancomycin and the need for appropriate serum monitoring. Monitoring is especially important in patients with renal impairment and/or other risk factors, as well as in patients who are being treated with the drug for a prolonged period.

Vancomycin is an amphoteric glycopeptide antimicrobial drug used to treat potentially life-threatening infections that cannot be effectively treated with another less toxic drug.

The TGA has reviewed a case report of vancomycin-induced nephrotoxicity, as clinically identified by increasing serum creatinine.<sup>1</sup> In this case, serum vancomycin was only tested at 11 hours and at cessation of treatment on day 10.

The authors of the report found that the nephrotoxicity might have been prevented if the vancomycin levels had been measured sooner. They have recommended that monitoring of serum vancomycin should be undertaken on day three of treatment.

Following the review of the case report, the TGA has found that the risk of this adverse event is well documented in the current Product Information (PI). Unmonitored and prolonged use of vancomycin administered in an intravenous infusion to a renally

compromised patient can result in severe and potentially irreversible nephrotoxicity. Obesity and being elderly are additional risk factors for vancomycin-induced nephrotoxicity.

The PI and the Australian Therapeutic Guidelines include advice for effective monitoring and dose adjustment of vancomycin. Monitoring is recommended for all patients treated with this drug for a prolonged period (more than 48–72 hours).

Health professionals should refer to these resources when treating patients with vancomycin to minimise the risk of nephrotoxicity.

As of 1 May 2013, the TGA had received 108 reports of adverse events classified as 'renal and urinary disorders' associated with vancomycin. The majority of the adverse event reports involved seriously ill patients, most of whom were treated with a wide variety of concomitant drugs, including some that were also potentially nephrotoxic. The degree of monitoring and dose adjustment that may have occurred in those cases is unknown.

The TGA is continuing to monitor this issue and health professionals are encouraged to report any adverse events relating to vancomycin and nephrotoxicity.

### REFERENCE

1. Jones TE, Vasileff H, Hewton C. Should monitoring of vancomycin be delayed? A case of likely nephrotoxicity occasioned by morbid obesity and minimal monitoring. *Br J Clin Pharmacol* 2012;74:1063-5.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

**TGA** Health Safety  
Regulation

## Dapagliflozin – new chemical entity

Dapagliflozin (Forxiga) is the first of a new class of drugs indicated for the treatment of type 2 diabetes. Health professionals are reminded to review the Product Information (PI) before prescribing and are encouraged to report all associated adverse events.

As part of the TGA's risk management approach, monitoring is most intensive for newly available drugs. Data gathered before a drug is registered may be limited, as these studies often involve small numbers of patients with few comorbidities.

### Drug information

Dapagliflozin is a selective and reversible inhibitor of the sodium-glucose co-transporter 2 (SGLT2). SGLT2 is responsible for approximately 90% of renal glucose reabsorption. Inhibition of SGLT2 increases glucose excretion, producing glycosuria, normally a feature of diabetes. This action has the potential to reduce hyperglycaemia.

Dapagliflozin can be used as monotherapy, as initial combination therapy with metformin, or as add-on combination therapy with metformin, a sulfonylurea or insulin (alone or with metformin and/or a sulfonylurea).

Dapagliflozin is contraindicated for patients with creatinine clearance of less than 60 mL/min or an estimated Glomerular Filtration Rate (eGFR) of less than 60 mL/min/1.73 m<sup>2</sup>. The efficacy of dapagliflozin is reduced in patients with impaired renal function and further renal deterioration is more common in this group.

Dapagliflozin's effects include:

- increased excretion of glucose in urine resulting in a modest decrease (placebo controlled) in HbA1c of approximately 0.6–0.7%, independent of insulin
- reduction in weight – 2 kg more than placebo over two years
- increased fluid excretion
- a small increase in serum parathyroid hormone levels.

### Risks

There is an identified risk of increased urinary tract and genital infections associated with treatment with dapagliflozin.

Other potential risks include:

- hypovolaemia, dehydration and hypotension
- increased haematocrit
- changes in bone mineral metabolism and bone fractures.

In premarket testing, the increase in haematocrit was common but small. Haematocrit greater than 55% or haemoglobin greater than 18 g/dL was reported in less than 2% of dapagliflozin subjects (less than 0.1% had haematocrit values greater than 60%).

Dapagliflozin has a diuretic effect. Consistent with this, small decreases in eGFR were seen as early as one week after administration of dapagliflozin. This trend reversed with time. The risk of renal impairment or failure depends on the baseline level of renal function. The proportions of subjects (dapagliflozin total vs placebo) with adverse events of renal impairment or failure in the mildly impaired subgroup eGFR  $\geq 60$  to  $< 90$  mL/min/1.73 m<sup>2</sup> were 13 (0.7%) versus 4 (0.5%). In the moderate renal impaired group  $\geq 30$  to  $< 60$  mL/min/1.73 m<sup>2</sup> they were 23 (8.3%) versus 6 (5.6%).

No interaction studies have been done with potentially nephrotoxic drugs, apart from mefenamic acid.

See dapagliflozin's Australian Public Assessment Report for further details.

### Monitoring

Monitoring of renal function is recommended:

- prior to initiation of dapagliflozin and at least yearly thereafter
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter
- for renal function approaching moderate renal impairment, at least two to four times per year and, if renal function falls below a creatinine clearance of  $< 60$  mL/min or eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>, treatment with dapagliflozin should be discontinued.

Special considerations for use in indigenous communities are:

- higher rates of type 2 diabetes
- higher prevalence of renal impairment
- remote locations making follow-up more difficult
- hot climates with higher risk of dehydration.

## Dexmedetomidine hydrochloride and cardiovascular events

Careful patient selection and consideration of the setting in which dexmedetomidine hydrochloride (Precedex) is used are crucial to ensuring its safe use. Following review of a recent investigational study involving off-label use of dexmedetomidine, the TGA is reminding health professionals that it should only be used for the approved indications and should be administered in accordance with the instructions in the Product Information (PI).

Dexmedetomidine is a relatively selective  $\alpha_2$ -adrenoceptor agonist used for sedation.

In an intensive care setting, dexmedetomidine is indicated for sedation of initially intubated patients. However, use of the drug by continuous infusion should not exceed 24 hours.

Dexmedetomidine is also indicated for procedural sedation. It can be used for non-intubated patients before and/or during surgeries and other procedures.

Dexmedetomidine's mechanism of action is unique compared with that of traditional sedatives because it does not act on gamma-aminobutyric acid receptors. The drug lacks anticholinergic activity, promotes a natural sleep pattern and does not cause respiratory depression.

The pattern of sedation is also different to commonly used sedatives, such as midazolam, in that patients can be wakened while sedated. This does not necessarily indicate a lack of efficacy.

It is important to note the slow action of dexmedetomidine. The full sedative effects of the drug may not be seen for 20–30 minutes after commencement of an infusion.

Atrial fibrillation, bradycardia and hypotension are all listed as adverse effects or precautions in the current PI for dexmedetomidine. There is a warning in the Precautions section regarding use in the elderly, in patients with high vagal tone, or chronic diseases, such as diabetes and heart failure, and with concomitant drugs with a similar pharmacological action.

In the past 10 years, the TGA has received a small number of spontaneous reports of cardiovascular events involving dexmedetomidine (of a kind listed as known adverse events in the PI).

### Emergency department study

A study conducted in 2012 aimed to investigate the safety and effectiveness of dexmedetomidine for emergency department patients with acute behavioural disturbance and who were difficult to sedate. The authors concluded that use of intravenous dexmedetomidine in such situations was unsafe.<sup>1</sup>

It is important to note that sedation of patients with an acute behavioural disturbance is not an approved indication for dexmedetomidine. Also, factors other than use of the drug may have contributed to the patient outcomes discussed in the study.

### Information for health professionals

Health professionals are reminded to carefully consider patient selection and the setting in which dexmedetomidine is administered to ensure its safe use. Dexmedetomidine should only be used for the approved indications and should be administered in accordance with the instructions in the PI.

A controlled infusion device should be used for the administration of dexmedetomidine, and the dose and rate of infusion should not exceed that recommended in the PI.

Particular caution is required in the following situations:

- patients with hypovolaemia, as dexmedetomidine decreases sympathetic nervous system activity
- patients with some level of autonomic system dysfunction, such as those with diabetes and the elderly
- patients of all ages with high vagal tone
- with concomitant use of vasodilators, negatively chronotropic agents, and/or other agents with  $\alpha_2$ -adrenoceptor agonist activity, such as clonidine and droperidol.

The TGA will continue to monitor dexmedetomidine and encourages health professionals to report all related cardiovascular adverse events.

### REFERENCE

1. Calver L, Isbister GK. Dexmedetomidine in the emergency department: assessing safety and effectiveness in difficult-to-sedate acute behavioural disturbance. *Emerg Med J* 2012;29:915-8.

## Bevacizumab and necrotising fasciitis

Health professionals are advised that the Product Information (PI) for bevacizumab (Avastin) has recently been updated to include a precaution about necrotising fasciitis.

Bevacizumab is an antineoplastic agent, a human monoclonal antibody that selectively binds and inhibits the biological activity of human vascular endothelial growth factor (VEGF). Inhibition of VEGF activity reduces the vascularisation of tumours, thereby hindering their growth.

Necrotising fasciitis is a life-threatening bacterial infection of the soft tissue. It is characterised by rapidly spreading necrosis of superficial fascia and subcutaneous tissue.

Symptoms may include sudden severe pain in the affected area; redness, heat, swelling, or fluid-filled blisters in the skin; scaling, peeling, or discoloured skin over the affected area; and fever. Other symptoms may include confusion, fainting or dizziness.

Internationally, necrotising fasciitis has been reported in a small number of patients receiving bevacizumab in both clinical trials and in the postmarket setting. Some of these cases have been fatal. There have been no reports of necrotising fasciitis in patients receiving bevacizumab in Australia.

The reported cases show occurrence of necrotising fasciitis in patients with several different types of cancers. However, it has been found that the incidence of the infection associated with bevacizumab is rare and usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.<sup>1</sup>

It is recommended that bevacizumab be discontinued and appropriate therapy initiated promptly upon diagnosis.

### REFERENCE

1. Health Canada. Avastin (bevacizumab) – cases of necrotizing fasciitis reported – for health professionals [Dear Healthcare Professional Letter]. 2013.



### What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies.

We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the October issue of *Australian Prescriber*
- **online** at [www.tga.gov.au](http://www.tga.gov.au)
- **by fax** to (02) 6232 8392
- **by email** to [ADR.Reports@tga.gov.au](mailto:ADR.Reports@tga.gov.au)

For more information about reporting, visit [www.tga.gov.au](http://www.tga.gov.au) or contact the TGA's Office of Product Review on 1800 044 114.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

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Medicines Safety Update is written by staff from the Office of Product Review

Editor:  
Dr Katherine Gray

Deputy Editor:  
Mr Michael Pittman

TGA Principal Medical  
Advisor:  
Dr Tony Hobbs

Contributors include:  
Dr Luigino Apollonio  
Ms Kushani Chandrasena  
Dr Rona Hiam  
Dr Kaye Robertson

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