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## Safe prescribing of metformin in diabetes

#### Peter Davoren

Director Diabetes and Endocrinology Gold Coast University Hospital

Associate professor Griffith University School of Medicine Southport

Queensland

#### Key words

biguanides, lactic acidosis, type 2 diabetes

Aust Prescr 2014;37:2-5

#### **SUMMARY**

Metformin is the first-line pharmacological therapy for type 2 diabetes. It is the only glucose-lowering oral drug that has been shown to reduce mortality in patients with diabetes.

The most common adverse effect is gastrointestinal upset. Starting at a low dose and increasing it slowly reduces this risk. Taking metformin with food also helps.

Numerous contraindications to the use of metformin are listed in the product information, including reduced renal function. Strict adherence to these recommendations may deny a valuable drug to many patients.

#### Introduction

Metformin lowers both fasting and postprandial blood glucose. It reduces hepatic glucose output<sup>1</sup> and increases peripheral glucose uptake, and may delay intestinal glucose absorption. Its use is not associated with weight gain and hypoglycaemia is extremely rare when metformin is used on its own. It lowers triglyceride concentrations and has small but beneficial effects on total and high-density lipoprotein cholesterol.

#### **Pharmacokinetics**

Metformin is absorbed throughout the gastrointestinal tract with an oral bioavailability of 50–60%. It is extensively distributed to the tissues. Metformin does not significantly bind to plasma proteins and reaches

#### **From the Editor**



Two new drugs for diabetes appear in this issue of *Australian Prescriber*. One of them is an inhibitor of the sodium-glucose co-transporter. Tilenka Thynne and Matt Doogue explain how this class of drugs works, and Timothy Davis discusses where the drugs may fit in the treatment of type 2 diabetes. According to Peter Davoren, metformin remains first-line therapy.

One of the adverse effects of inhibiting the sodiumglucose co-transporter is infection in the urinary tract. Thomas Jarvis, Lewis Chan and Thomas Gottlieb advise on how to treat lower urinary tract infections in adults. Bladder dysfunction can result in incontinence. Shannon Kim, Shuo Liu and Vincent Tse say how this can be managed. a steady state in 24–48 hours. The plasma half-life is around 3.5 hours. Metformin does not undergo hepatic metabolism and over 90% of the drug is excreted unchanged in the urine.

#### **Clinical use**

In the UK Prospective Diabetes Study metformin reduced diabetes-related and all-cause mortality, and reduced the risk of myocardial infarction in obese patients with type 2 diabetes when used as first-line therapy. It also reduced the risk of microvascular complications, but was no more effective than insulin or sulfonylureas.<sup>2</sup> A retrospective cohort study from the USA found a lower rate of hospitalisations for myocardial infarction and stroke and a reduced death rate when metformin was used first-line in type 2 diabetes in comparison with a sulfonylurea.<sup>3</sup>

Metformin is effective when used with other glucoselowering drugs. A standard-release (3000 mg/day maximum dose) and an extended-release preparation of metformin (2000 mg/day maximum dose) are available. The extended-release preparation can be taken once daily.

#### **Contraindications and cautions**

As our knowledge of metformin has improved, many cautions have become outdated. Proposed changes to the current contraindications are shown in the Table. According to the product information, metformin is contraindicated in patients with a creatinine clearance less than 60 mL/min, moderate-severe heart failure, acute myocardial infarction, and those undergoing major surgery.

The level of renal function at which metformin becomes unsafe is not clear. Many prescribers use metformin in patients with impaired renal function. A creatinine clearance of 30 mL/min may be an appropriate level at which to consider stopping the drug, although some patients may tolerate small doses with less renal function. Patients with impaired renal function should suspend metformin if they develop vomiting, febrile illness, diarrhoea or poor tissue perfusion. There is no place for routinely measuring serum lactate to determine the safety of metformin as this does not predict those at risk of lactic acidosis.<sup>4</sup>

Evidence suggests that, if anything, metformin may be beneficial in people with heart failure.<sup>5</sup> The degree of heart failure may not predict the likelihood of benefit. Metformin should not be prescribed in those with symptomatic heart failure at rest or with minimal exertion where the goals of glucose control are different from those of more mobile patients.

Patients with otherwise reasonable overall health can probably take metformin in the presence of renal disease, heart disease or other underlying comorbid conditions. The metformin dose can be reduced depending on the severity of the comorbid conditions and patients should be advised to suspend the drug if they develop any acute illness predisposing them to dehydration or poor tissue perfusion.

The use of metformin around the time of surgery and other acute illnesses requiring hospital admission should be determined by the presence or risk of renal dysfunction or an infection. Metformin may need to be suspended temporarily.

#### Pregnancy

Despite metformin being a category C drug in pregnancy, data are reassuring in terms of the risk of congenital anomalies.<sup>6,7</sup> The product information recommends that metformin be replaced with insulin. However, data do not support this.

Hyperglycaemia is a recognised teratogen and stopping metformin when pregnancy is discovered (with or without the introduction of insulin) often results in significant hyperglycaemia, a state more

associated with abnormal blood glucose levels

dangerous than continuing the metformin. Metformin can be continued while adjusting the insulin dose. Many diabetes physicians continue metformin throughout pregnancy, only stopping the drug if pre-eclampsia develops.

#### Gestational diabetes

A large randomised trial has demonstrated that metformin is a valid alternative to insulin in gestational diabetes. Perinatal outcomes were similar, although the trial was not powered to detect differences in perinatal mortality.<sup>8</sup>

#### Lactation

The product information does not recommend metformin during lactation. However, as in pregnancy, the available data do not support withholding metformin in breastfeeding women.

Infants receive approximately a 0.2% weight-adjusted dose of metformin if the mother is breastfeeding. The concentration of metformin in breast milk is probably relatively constant and so timing doses after breastfeeding probably does not alter exposure.<sup>9</sup>

#### **Gastrointestinal adverse effects**

Nausea, vomiting, abdominal bloating, diarrhoea, anorexia and abdominal pain are the most common

#### Table Proposed changes to product information for metformin

Current information in product information	Proposed change
Contraindications	
Renal failure or renal dysfunction	Reduce dose for creatinine clearance 30–60 mL/min
(creatinine clearance <60 mL/min)	Use with caution and close supervision if creatinine clearance <30 mL/min in selected patients
Acute conditions with the potential to alter renal function, such as dehydration, severe infection, shock, intravascular administration of iodinated contrast media	Suspend metformin during acute conditions with the potential to alter renal function, including dehydration, severe infection, shock, intravascular administration of iodinated contrast media (>100 mL contrast in patients with normal renal function) until patient's condition is stable
Acute or chronic disease which may cause tissue hypoxia, such as cardiac failure, recent myocardial infarction, respiratory failure, pulmonary embolism, shock, acute significant blood loss, sepsis,	Suspend metformin during acute diseases which may cause tissue hypoxia, pulmonary embolism, shock, acute significant blood loss, sepsis, gangrene or pancreatitis until patient's condition is stable
gangrene, pancreatitis	Cardiac failure and chronic respiratory failure should be removed as contraindications
Elective major surgery	Can be continued perioperatively if renal function stable
	Suspend if acute complications
Cautions	
Lactation	Safe to use
Pregnancy (Category C)	Fetal malformations associated with abnormal blood glucose levels are best prevented
When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but	by good blood glucose control. If metformin is the best drug to achieve control it can be used.
insulin should be used to maintain blood glucose levels as close to normal as possible, to lower the risk of fetal malformations	Abruptly stopping metformin when pregnancy is discovered can result in sudden deterioration in blood glucose control.

#### ARTICLE

Safe prescribing of metformin in diabetes

adverse effects of metformin. Symptoms are often self-limiting, but are persistent in some patients. Metformin should be commenced at a low dose (500 mg/day) and always with food, to reduce the risk of gastrointestinal adverse effects. The dose should be escalated slowly. It is not uncommon for a

metformin should be taken with food to reduce gastrointestinal adverse effects

patient who has tolerated metformin for many years to develop gastrointestinal adverse effects. It is appropriate to stop metformin in any patient who develops gastrointestinal upset to determine if metformin is the culprit. In a retrospective study, gastrointestinal effects were half as likely to occur with extended-release metformin compared with standard metformin.<sup>10</sup>

#### Vitamin B<sub>12</sub> malabsorption

Metformin causes vitamin B<sub>12</sub> malabsorption in some patients. In a placebo-controlled trial, vitamin B<sub>12</sub> concentrations below the reference range were observed in 18.2% of patients taking metformin and vitamin B<sub>12</sub> deficiency was seen in almost 10% (after four years). This was considerably higher than in the control group.<sup>11</sup> It is prudent to measure vitamin B<sub>12</sub> yearly in patients taking metformin, and prescribe vitamin B<sub>12</sub> if concentrations are below the reference range.

#### Lactic acidosis

Lactic acidosis is an adaptive physiologic response by the body to energy failure, so that cells may survive. When individuals develop conditions resulting in reduced tissue perfusion and hypoxaemia, lactate will be produced and acidosis will occur as part of the body's compensatory response.

Metformin is plagued by its association with the similar drug phenformin, which was withdrawn from the market many years ago because of its association with lactic acidosis.<sup>12</sup> Phenformin is thought to reduce peripheral glucose oxidation and therefore increase circulating lactate. This is not observed with metformin.<sup>13</sup> In a Cochrane review, the estimated upper limit for the incidence of lactic acidosis in metformin users was 4.3 cases per 100 000 patient-years compared with 5.4 cases per 100 000 patient-years in those assigned to other treatment groups.<sup>14</sup>

Many publications indicate that metformin is frequently prescribed to patients with contraindications. However, there are intermittent reports of fatal lactic acidosis. These fatalities

are nearly always associated with the use of intravascular iodinated contrast media for radiological investigations. Such patients commonly have underlying renal disease and develop acute renal failure in association with the use of contrast media and then develop marked metformin accumulation.<sup>15</sup> Stopping metformin temporarily for the investigation should diminish the risk of lactic acidosis. However, there is much disagreement as to the appropriate schedule to follow.<sup>16</sup> The Royal Australian and New Zealand College of Radiologists recommends no withdrawal of metformin in patients with normal renal function and contrast doses up to 100 mL. Patients with impaired renal function should suspend metformin for 48 hours from the day of the procedure and recommence when a test of renal function shows no deterioration.<sup>17</sup> In patients undergoing urgent investigations, adequate intravenous hydration should be maintained to preserve renal function. Prolonged withdrawal of metformin may lead to hyperglycaemia and consequent dehydration. This may cause acute deterioration in renal function in patients with diabetes and pre-existing renal disease.

#### **Pre-diabetes**

In a randomised trial, metformin reduced the risk of developing type 2 diabetes by around 30% in highrisk patients. However in the same study, interventions with diet and exercise were twice as effective as metformin in preventing diabetes.<sup>18</sup>

#### Conclusion

Metformin is the drug of first choice in the management of hyperglycaemia in type 2 diabetes. It improves mortality in obese patients with diabetes. The risk of gastrointestinal adverse effects is common. In patients with diabetes, the risk of lactic acidosis in metformin users does not appear to be higher than in non-users. However, the use of intravascular iodinated contrast material in association with metformin may pose the greatest risk of lactic acidosis.

Metformin can be continued despite some of the contraindications in the product information if the dose is reduced in appropriate patients and stopped at the time of acute illness. Warnings about the use of metformin in pregnancy and breastfeeding should be reviewed.

Conflict of interest: none declared

#### SELF-TEST **QUESTIONS**

True or false? 1. Metformin is always contraindicated in lactation.

2. Vitamin B<sub>12</sub> should be measured periodically in patients taking metformin.

Answers on page 35

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# Letters to the Editor

#### **Rational use of topical corticosteroids**

Editor, – In the article on topical corticosteroids (Aust Prescr 2013;36:158-61) there is no reference to the oral mucosa. Some steroid preparations have long been used as effective treatment for conditions in the mouth, notably for lichen planus.<sup>1</sup> One option is 0.05% betamethasone ointment. This has proved particularly relevant in over 20 years of practice, as I am contacted periodically by pharmacists questioning if such a prescription is appropriate for use on the oral mucosa.

Angus Kingon Oral surgeon Pymble, NSW

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### Pablo Fernández-Peñas, one of the authors of the article, comments:

Some mucosas have stratified epithelium similar to the skin, but with thinner or nonexistent stratum corneum. This changes the absorption of molecules. In a cream or ointment there are more components than the corticosteroid, and I do not have enough information to assess that it is safe to use skin products in the oral mucosa.

The clinical outcome will depend on making a correct diagnosis and applying the right molecule in the most appropriate vehicle for the correct duration. In this regard, there may be vehicles that are not adequate for the oral mucosa. Most dermatologists tend to compound their topical corticosteroids in 'orabase' for use on mucosas, to be on the safe side.

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The Editorial Executive Committee welcomes letters. which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Committee screens out discourteous inaccurate or libellous statements and sub-edits letters before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

## Asthma drugs in pregnancy and lactation

Editor, – The article 'Asthma drugs in pregnancy and lactation' (Aust Prescr 2013;36:150-3) was informative and well written, but there was one omission. While there is a role for 'doctors, pharmacists, asthma educators and midwives in encouraging adherence to treatment', equally important is the role of the registered nurse providing education and support in treatment management. In particular, the registered nurse endorsed as a nurse practitioner may act in this capacity.

Depending on their scope of practice, nurse practitioners may be primary care providers, actively involved and independently responsible for prescribing and management of medication regimens for pregnant women with asthma. Primary care has been identified as a key growth area for nurse practitioners working to improve access to care and improve effectiveness and efficiency of the healthcare system.<sup>1,2</sup> As of June 2013, there were 926 endorsed nurse practitioners registered with the Nursing and Midwifery Board of Australia.<sup>3</sup>

Jane E Truscott

Nurse practitioner Acute Care/Primary Health Care Independent Clinical Education Consultant Regional and rural Qld

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#### Angelina Lim, Safeera Hussainy and Michael Abramson, the authors of the article, comment:

We agree and advocate that nurse practitioners have a vital role in counselling and improving adherence and ongoing asthma monitoring during pregnancy. It is important that the allied health community work together to provide multidisciplinary care for our patients.

We are preparing to report a study that showed an intervention including multidisciplinary care, education and regular monitoring can help improve asthma control in pregnant women. (The protocol is available at www.biomedcentral.com/1471-2458/12/ 1094.) The study was in an antenatal setting and mainly involved midwives, however we recently conducted a survey which found many GPs are working with nurse practitioners to help provide better asthma management. After disseminating our results from this trial, we hope to encourage regular monitoring of maternal asthma in the community and make good use of nurse practitioners too.

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# Assessment and management of lower urinary tract infection in adults

#### SUMMARY

Lower urinary tract infections are common in the community and in hospitals.

Management of acute uncomplicated infections in non-pregnant women is usually simple and involves antibiotic treatment for 3–5 days.

Infections in men and recurrent, drugresistant or complicated urinary tract infections require further evaluation. Confirming the cause is important to ensure the best treatment.

Because of the risk of antibiotic resistance, asymptomatic bacteriuria should only be treated in select groups such as pregnant women and those undergoing an invasive genitourinary procedure. Bacteriuria in patients with a catheter should only be treated if they are symptomatic.

#### Introduction

Lower urinary tract infections are responsible for a large number of presentations in general practice and frequent antibiotic prescriptions. They also cause significant financial strain on health services.<sup>1</sup> For females, there is a one-in-three lifetime incidence of urinary tract infection (approximately 50 times more than for males). Prevalence increases with age in men and women.<sup>2</sup>

#### Pathogenesis

Lower urinary tract infections generally present as cystitis, which is an infection of the superficial bladder mucosa. Ascending access via the urethra is the most common mechanism by which pathogens such as *Escherichia coli* infect the bladder. *E. coli* accounts for 80–90% of infections. Other pathogens include *Staphylococcus saprophyticus* (5–10%), enterococci, *Proteus mirabilis* and other enteric Gramnegative rods such as *Klebsiella* species. Spread from a haematogenous source is rare, but is seen with organisms such as *Staphylococcus aureus*, *Salmonella* species and *Mycobacterium tuberculosis*. While virulence factors play a role in the ability of a pathogen to cause an infection (such as pili which facilitate bacterial ascent), most important are the body's natural defence mechanisms. These may be compromised in patients with diabetes, immunosuppression, urinary stone disease, some connective tissue diseases, hypo-oestrogenic states such as atrophic vaginitis in women, and bladder outlet obstruction from prostatic enlargement or stricture disease in men. Indwelling catheters are a common cause of bacterial colonisation and urinary tract infections.

#### Presentation

The presenting features of lower urinary tract infection include frequent urination or an urgent need to urinate, dysuria, suprapubic pain and turbid or foul smelling urine. Fever and non-specific lower back pain may be present. Loin pain accompanied by systemic symptoms such as fevers, rigors, nausea and vomiting may suggest an ascending infection or pyelonephritis. In elderly patients, confusion may be the only presenting symptom.

Symptoms consistent with cystitis may not always be due to infection. The differential diagnoses are numerous and include pelvic inflammatory disease, sexually transmitted diseases, urothelial carcinoma and bladder calculi. This highlights the importance of careful diagnosis and follow-up.

#### Initial evaluation of the patient

Urinary tract infections are classified by severity to aid clinical management.<sup>3</sup> The aim of the history, examination and investigations should be to identify patients with complicated urinary tract infections or patients with risk factors who may require specific investigations or more prolonged treatment. An 'uncomplicated' urinary tract infection is one in which there are no structural or functional abnormalities within the urinary tract. A physical examination includes checking vital signs, as well as abdominal and flank examination. When required, external genital examination may show atrophic vaginitis in females and phimosis or meatal stenosis in men. Rectal examination may reveal an enlarged prostate or tenderness to suggest acute prostatitis in males. A urine dipstick (e.g. for nitrites, leukocyte esterases) can indicate the presence of a urinary tract infection.

#### Thomas R Jarvis

Clinical associate lecturer Workforce Education and Development Group Sydney Medical School<sup>1</sup>

#### Lewis Chan

Staff specialist in Urology Concord Repatriation General Hospital Clinical associate professor (Surgery) Concord Clinical School<sup>1</sup>

#### **Thomas Gottlieb**

Clinical associate professor Medicine (Immunology and Infectious Diseases) Concord Clinical School<sup>1</sup>

<sup>1</sup> The University of Sydney

#### Key words

antibiotics, bacteriuria, catheters, cystitis

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#### ARTICLE

#### Assessment and management of lower urinary tract infection in adults



#### Investigations

Antibiotic treatment may be commenced empirically for symptomatic cystitis if clinically warranted. However, formal microscopy, culture and susceptibility testing should be performed in most circumstances to ensure patients receive appropriate antimicrobial therapy, especially given the rising incidence of antibiotic resistance. This is particularly important in men, pregnant women and patients with recurrent infections.

A midstream urine is considered clinically positive if there are more than  $10^3$  colony forming units (cfu)/mL in acute uncomplicated infections in women. In complicated urinary tract infections, more than  $10^5$  cfu/mL in a midstream sample of urine in women and more than  $10^4$  cfu/mL in men or in an in-out catheter urine in women are clinically significant.<sup>1</sup> There is usually an associated pyuria (>100 white blood cells/ high power field). Contamination of the sample with epithelial cells is indicative of poor collection technique. Blood cultures should be taken if the patient has signs of sepsis or has an unusual organism in the urine, such as *S. aureus*, suggesting a haematogenous source.

Ultrasound of the urinary tract is indicated in patients with recurrent infections to check for upper tract abnormalities and urinary stones. It is also indicated in older men to check for bladder outlet obstruction and residual urine volume post-voiding. Patients with macroscopic haematuria or persistent microscopic haematuria following resolution of a urinary tract infection should have a cystoscopy and evaluation of the upper tracts. This is usually done with a CT urogram.

#### Treatment

Most urinary tract infections require antibiotics. However, there is progressive development of antimicrobial resistance to common antibiotics in Australia and overseas. Extended-spectrum betalactamase producing *E. coli* showing resistance to most antibiotics (except for the carbapenem class), are becoming more common.<sup>4</sup> In some parts of the world, such as China and the Indian subcontinent, up to 80% of *E. coli* produce extended-spectrum beta lactamases.<sup>5</sup> These strains are now increasingly seen locally in the elderly, especially those in long-term care facilities. Antibiotic choice is therefore guided by knowledge of local resistance patterns.

#### Uncomplicated urinary tract infections

Uncomplicated infections should almost always be treated with antibiotics to decrease duration and severity of symptoms.<sup>6</sup> In Australia, trimethoprim, cephalexin, or amoxycillin with clavulanate can be used for the majority of acute, uncomplicated

infections, in the absence of previous antibiotic exposure or other risk factors such as recent travel to high-risk areas. Nitrofurantoin is an option in shortcourse therapy for cystitis, especially when drug resistance is present. However, long-term use should be avoided, especially in older patients as peripheral neuropathy can occur with impaired renal function. Fluroquinolones (for example norfloxacin and ciprofloxacin) should be considered second-line and restricted to patients with culture-proven resistant organisms. A 3–5 day course of therapy is associated with good outcomes for uncomplicated infections.

#### Recurrent urinary tract infections

Clinicians should confirm the diagnosis and look for a cause in adults with recurrent urinary tract infections. Risk factors include sexual activity (including anal intercourse), contraceptive devices (such as intrauterine devices), hormonal deficiency in postmenopausal women, diabetes, foreign objects (including bladder calculi), secretory type of certain blood groups<sup>7</sup> and urinary tract obstruction (including benign prostatic hyperplasia or pelvic organ prolapse). Recurrent infections can be due to bacterial persistence or re-infections. It is important to have an adequate course of antibiotics and repeat urine microscopy, culture and susceptibility tests after treatment is completed to ensure clearance of the organism. Consider an ultrasound of the urinary tract to exclude structural abnormality and document complete bladder emptying. Therapeutic strategies include low-dose antibiotic prophylaxis and patient-initiated antibiotics guided by symptoms, although this should be only undertaken following comprehensive assessment as long-term antibiotics should preferably be avoided.

#### Strategies to prevent recurrence

Topical vaginal oestrogen therapy (especially in the presence of atrophic vaginitis) and alkalysing agents may provide symptomatic relief and are often used as preventive strategies. However, they do not necessarily have any impact on reducing recurrent infections. Cranberry in the form of tablets and juice is often advocated for prevention but may not be effective.<sup>8</sup> If recurrence is associated with sexual activity, advise bladder emptying immediately after sex.

#### Complicated urinary tract infections

When there is known or suspected stone disease, pyelonephritis, prostatitis, (epididymo)orchitis or neurogenic bladder, further evaluation is recommended to exclude anatomical abnormalities and urinary obstruction that may need surgery. Infections associated with urinary tract obstruction, such as pyelonephritis due to an obstructing ureteric stone, are a medical emergency. These patients require urgent hospital admission and surgical drainage with placement of a nephrostomy tube or ureteric stenting. It is important that patients with complicated urinary tract infections are prescribed an adequate course of antibiotics – usually for at least 10–14 days. Therapy should be guided by culture results.

#### Asymptomatic patients

There is evidence to warrant screening and treatment of pregnant women for asymptomatic bacteriuria due to the risk of pyelonephritis causing preterm birth and low birth weight babies.<sup>9</sup> Similarly, patients undergoing an invasive genitourinary procedure, such as a transurethral resection of the prostate, should have urine microscopy, culture and susceptibility tests pre-operatively.

There is no evidence that other patients should be routinely screened or treated for asymptomatic bacteriuria, including those with indwelling catheters, nursing home residents, women after menopause, the elderly, patients with diabetes or a spinal injury, or men with increased post-void residual volumes. In fact, treating asymptomatic infection is likely to increase the chance of developing an antibiotic-resistant infection.

#### Patients with a catheter

The urinary tract is the most common source of nosocomial infection, especially in patients with catheters.<sup>10</sup> In these patients, bacteriuria is expected within a few days due to colonisation, although in the short term it is usually asymptomatic and from a single organism. Catheterisation for longer than 30 days is associated with colonisation with multiple organisms.

Catheterised patients with bacteriuria should only be treated if they are symptomatic or about to undergo a urological procedure. Such signs or symptoms may include fever, rigors, altered mental status, malaise, lethargy with no other identified cause, flank pain, acute haematuria, or pelvic discomfort. Pyuria alone is not diagnostic of catheter-associated infection.<sup>11</sup> The catheter should be changed at the time of antibiotic treatment.

Recurrent catheter-associated urinary tract infection may be reduced by careful catheter handling and management, removal of unnecessary catheters, and changing to a suprapubic catheter. The use of silver impregnated catheters seems only to decrease colonisation within the first week, although there has been some evidence they may reduce the risk of symptomatic urinary tract infection.<sup>12</sup> There is a role for low-dose prophylactic antibiotics in patients susceptible to severe infections or sepsis after common causes for recurrence, such as poor catheter care or bladder calculi, have been excluded. This should generally only be undertaken with specialist input due to the risks of long-term antibiotic use.

#### Conclusion

Most lower urinary tract infections are easy to identify and treat. However, with the rise in multiresistant organisms, the more challenging cases require careful consideration, investigation and discussion with a urologist or microbiologist rather than further prescription of empirical antibiotics.

Conflict of interest: none declared

#### SELF-TEST QUESTIONS

True or false?

3. Fluroquinolones are first-line treatment for uncomplicated urinary tract infections.

4. Complicated urinary tract infections should be treated for at least 10–14 days with antibiotics.

Answers on page 35

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# Management of urinary incontinence in adults

**Shannon Kim** Urology registrar<sup>1</sup>

**Shuo Liu** Urology resident<sup>1</sup>

Vincent Tse Urologist<sup>1</sup> Clinical senior lecturer<sup>2</sup>

<sup>1</sup>Department of Urology Concord Repatriation General Hospital Sydney <sup>2</sup>Concord Clinical School University of Sydney

Key words

antimuscarinic drugs, benign prostatic hypertrophy, bladder

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#### **SUMMARY**

The two functions of the bladder are storing and voiding urine. Dysfunction of either can cause incontinence.

Urgency incontinence is a storage dysfunction most often associated with detrusor overactivity. It can be managed by bladder training and antimuscarinic drugs.

Stress incontinence is a storage dysfunction most often associated with poor ligamentous support of the pelvic floor or sphincter deficiency, or both. Drugs have a very limited role in treatment. Surgery is often needed.

Voiding dysfunction can be caused by bladder outlet obstruction, such as benign prostatic hyperplasia. Drug treatment may include alpha blockers.

Drugs for incontinence only have modest efficacy. They can have adverse effects away from the urinary tract, which may be particularly problematic in older people.

#### Introduction

The bladder has two functions: it stores and voids urine. Bladder dysfunction can therefore be broadly classified into storage and voiding dysfunction.

Storage dysfunction often presents with symptoms such as frequency, urgency, urgency incontinence and nocturia. Voiding dysfunction causes hesitancy, poor flow, terminal dribbling and incomplete emptying.<sup>1</sup> Storage and voiding dysfunction can each be further subclassified into bladder and outlet factors. For example, stress incontinence is a storage dysfunction caused by an outlet factor.

Obtaining a thorough history outlining the storage and voiding dysfunction is crucial to narrow the diagnosis of voiding dysfunction and identify the types of incontinence.

Although incontinence is not life threatening, patients with urinary incontinence have a reduced quality of life. The goal of treatment is to improve this either via drugs or surgery. The end point is improving quality of life by reducing symptoms (such as frequency, urgency, nocturia, incontinence). This is often more realistic than rendering the patient completely continent and should be made clear to patients from the outset.

#### Non-pharmacological treatment

Although continence appliances such as pads are the least invasive intervention, in general they are not the most preferred option. They may be accepted by patients who are not candidates for drug or surgical intervention (for example the very frail elderly) or in those who do not want drug or surgical treatment.

# Incontinence from storage dysfunction

Urgency and stress incontinence are the most common symptoms of bladder storage dysfunction.

#### Bladder factor - urgency incontinence

Apart from urinary tract infection the most common cause of urgency incontinence is the overactive bladder syndrome. This syndrome has urgency as its pivotal symptom, although it may also be associated with frequency and nocturia.

There are many causes of overactive bladder syndrome and they can be divided into neurogenic and non-neurogenic causes. Neurogenic overactive bladder can be associated with spinal cord injury, Parkinson's disease, multiple sclerosis and diabetes. In non-neurogenic overactive bladder syndrome, urinary tract infection and bladder malignancy must be ruled out along with foreign bodies such as bladder stones. Age-related overactive bladder and idiopathic detrusor overactivity should be considered. Also look for outlet factors such as benign prostatic hypertrophy or atrophic vaginitis.

The initial assessment requires a thorough history and examination. The assessment focuses on the duration, severity and inconvenience of the overactive bladder syndrome, the presence of other lower urinary tract symptoms especially haematuria, as well as past urological, neurological, and obstetric or gynaecological history. Feel for a palpable bladder and examine the prostate or vagina and test for stress incontinence with coughing and for pelvic organ prolapse. Examination of the S2-S4 nerve segment, for example by testing the bulbocavernosal reflex and anal tone, is vital to exclude occult neuropathology. A midstream urinalysis and culture, and measurement of the post-void residual urine volume is mandatory. A shorter onset of symptoms (for example less than three months), haematuria, or a history of heavy smoking may suggest urinary tract malignancy and will require further tests such as urine cytology, imaging and a referral to a urologist.

#### Treatment

There is little difference in drug therapy for neurogenic or non-neurogenic overactive bladder syndrome, with the mainstay being antimuscarinic drugs. When there is a low index of suspicion for cancer, empirical drug treatment with an antimuscarinic drug is reasonable. In idiopathic overactive bladder syndrome, the addition of bladder training to antimuscarinics is more effective than either treatment alone.<sup>2</sup>

Bladder training involves modifying lifestyle and fluid intake, pelvic floor muscle training, and postponement and distraction techniques.<sup>3</sup> Lifestyle modification includes losing weight, regular exercise and avoiding bladder irritants such as cigarettes and caffeine. A continence nurse specialist and physiotherapist should have the necessary expertise to assist with this training. The Continence Foundation of Australia also provides brochures free of charge to patients and healthcare professionals (www.continence.org.au).

Psychogenic factors and their drug treatment may be associated with lower urinary tract symptoms and incontinence. If diagnosed, some patients may respond to cognitive behavioural therapy.

There are five subtypes of muscarinic receptors. The detrusor and urothelium contain mainly M2 and M3 receptors. Although M2 receptors account for 80% of the receptors in the urinary tract, M3 receptors are primarily responsible for bladder contraction.<sup>4</sup> Antimuscarinic drugs can be classified as M3-selective or non-selective. Most of the current drugs produce varying degrees of common antimuscarinic adverse effects such as dry mouth, blurred vision, confusion, constipation and rarely tachycardia.<sup>4</sup> As the drugs have modest efficacy the patient needs to decide if the benefits outweigh these adverse effects. One less micturition may not be relevant to a patient who is having 12 episodes every day.

#### Non-selective antimuscarinics

Muscarinic receptors are found in gut and salivary glands, so non-selective drugs act on them as well as on the bladder.

#### Oxybutynin

Oxybutynin is available in both oral and transdermal patch formulations.<sup>5</sup> It can cross the blood-brain

barrier leading to adverse effects such as dizziness and cognitive dysfunction.

#### Tolterodine

Tolterodine has greater specificity for bladder receptors than for salivary glands. This has contributed to reports that it causes significantly less dry mouth than oxybutynin.<sup>6</sup> When tolterodine was compared to oxybutynin it had better tolerability, but there was no statistically significant difference in quality of life.<sup>7</sup>

#### M3-selective antimuscarinics

These drugs mainly act on bladder muscle.

#### Solifenacin

As solifenacin blocks M3 receptors, there is a lower rate of dry mouth and constipation than with non-selective antimuscarinic drugs.<sup>4</sup> An initial dose of 5 mg daily can be increased to 10 mg daily. In clinical trials, solifenacin reduced the daily mean number of voids compared to placebo (2.2 vs 1.2 episodes). The reduction in the number of urgency episodes is 2.8 with 5 mg solifenacin, and 1.4 with placebo, while the urgency incontinence episodes reduced by 1.4 per day compared to 0.5 per day with placebo.<sup>4</sup> While frequency and urgency were less commonly reported at a dose of 10 mg, there was an increased risk of dry mouth at 4–12 weeks.<sup>7</sup> Solifenacin is relatively safe in patients over 65 years old.<sup>8</sup>

#### Darifenacin

Darifenacin 7.5 mg significantly reduces the number of incontinence episodes per week, with a median reduction of two episodes compared to placebo. The most common adverse events in placebo-controlled 12-week trials were dry mouth and constipation. As darifenacin is metabolised by the liver it is not recommended for patients with severe liver impairment.<sup>4</sup>

#### Botulinum toxin

Randomised controlled trials show that an injection of botulinum toxin type A into the bladder wall is effective in both drug-refractory non-neurogenic and neurogenic overactive bladder syndrome.<sup>9</sup> The toxin inhibits the release of acetylcholine into the neuromuscular junction, thus dampening detrusor contractility. It reduces the frequency of micturition and the number of episodes of urgency incontinence, and increases functional bladder capacity and quality of life. The main potential adverse effects are temporary urinary retention that may require catheterisation, and urinary tract infection.

Botulinum toxin injections are given into the detrusor muscle during cystoscopy. Patients do require

#### Management of urinary incontinence in adults

repeated injections after a mean of 6–9 months due to loss of efficacy.

Recent approval was granted in the USA for the use of the toxin in both drug-refractory neurogenic and nonneurogenic overactive bladder syndrome. In Australia botulinum toxin A is approved by the Therapeutic Goods Administration for both neurogenic and nonneurogenic overactive bladder, with the neurogenic indication now listed on the Pharmaceutical Benefits Scheme.

#### Outlet factor – stress incontinence

The most common storage dysfunction related to an outlet factor is stress incontinence. It is due to intra-abdominal pressure exceeding urethral closure pressure, causing involuntary loss of urine. If pelvic floor muscular training fails, the mainstay of treatment is surgery, although lifestyle modifications (for example weight loss) and controlling comorbidities which put chronic strain on the pelvis (for example chronic obstructive pulmonary disease) may have a supportive role.

Effective surgical options for stress incontinence include the synthetic mid-urethral sling and autologous fascial slings in women, and the transobturator bulbo-urethral sling in men. Implantation of an artificial urinary sphincter can be tried if sling surgery fails.

The role for drug therapy in stress incontinence is very limited. Duloxetine, which is a serotonin and noradrenaline reuptake inhibitor, has some effects on increasing bladder outlet resistance. It has been effective in controlling mild urinary stress incontinence in women,<sup>4</sup> but it is not approved for this indication in Australia.

# Incontinence from voiding dysfunction

The detrusor muscle is relaxed when urine is stored. It contracts to overcome the resistance of the bladder outlet during voiding.

#### Overflow incontinence

Leakage of urine can be associated with urinary retention. This may be caused by poor detrusor contractility or be secondary to chronic bladder outlet obstruction.

# Incontinence associated with benign prostatic hyperplasia (outlet factor)

Chronic bladder outlet obstruction leads to functional changes, such as decreased bladder compliance and detrusor overactivity. In turn, this may result in frequency, urgency and urgency incontinence.<sup>10</sup> Detrusor overactivity, mediated by M2 and M3 muscarinic receptors, contributes to lower urinary tract symptoms in approximately 15% of men.<sup>11</sup> In patients with overactive bladder syndrome secondary to bladder outlet obstruction, treatment varies from watchful waiting to drug therapy and various surgical options depending on the severity of symptoms and indications for intervention.<sup>11</sup> The mainstay of drug treatment includes alpha adrenergic receptor blockers and 5-alpha-reductase inhibitors. If the overactive bladder syndrome is secondary to bladder outlet obstruction there may be a role for combinations of these drugs. Although there is a risk of acute urinary retention with alpha adrenergic receptor blockers and antimuscarinic drugs in combination, the rate is low.<sup>12</sup>

With 5-alpha-reductase inhibitors, common adverse effects include fatigue, loss of libido and ejaculatory and/or erectile dysfunction. Long-term use at the end of four years shows an absolute reduction in the overall risk of developing prostate cancer.<sup>13</sup> The alpha blockers can cause hypotension. As the elderly are more susceptible to orthostatic hypotension, they may have an increased risk of falls.

#### Incontinence in the elderly

Using drugs to manage incontinence in the elderly follows the basic prescribing principle of 'start low, go slow'. As well as the dose, polypharmacy and coexisting medical comorbidities must be considered.

Antimuscarinics such as oxybutynin and tolterodine are the mainstay for bladder overactivity, but should be used with care. The risk of urinary retention is a concern, as the ageing bladder is often associated with impaired emptying. This necessitates a slow escalation of the dose, frequent review of the response and monitoring of urine output and post-void residual volume.

Newer drugs such as darifenacin and solifenacin are more M3-selective and cross the blood-brain barrier less readily than non-selective drugs. There is some evidence that non-selective drugs are more likely to cause cognitive dysfunction.<sup>14</sup> The most recent randomised trial (2013 SENIOR trial) reports that both oxybutynin and solifenacin are well-tolerated in the elderly, but oxybutynin is associated with a reduction in attention compared to placebo.<sup>15</sup>

Detrusor hyperactivity with impaired contractility is a common but lesser known cause of incontinence in older people. Detrusor dysfunction results in both storage and the emptying dysfunction.<sup>16</sup> The clinical diagnosis is difficult and the management of this condition may require urological referral and urodynamic evaluation. Combination therapy with an anticholinergic and alpha, blocker can be efficacious by targeting both components of detrusor hyperactivity and impaired contractility.

#### Conclusion

Understanding the biphasic storage and voiding functions of the bladder helps diagnose and treat overactive bladder with or without incontinence.

The mainstay of overactive bladder management is pharmacological and is evolving. Newer treatments such as intravesical botulinum toxin injections are being used in neurogenic and non-neurogenic overactive bladders. Treatment is best delivered by a multidisciplinary approach via medical, nursing and physiotherapy personnel.

Vincent Tse is a consultant for Astellas.

Shannon Kim and Shuo Liu: no conflict of interest declared.

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#### Patient Support Organisation

#### **Continence Foundation of Australia**

The Continence Foundation promotes bladder and bowel health and the management of incontinence. It provides support and information about incontinence products and treatment for men, women and children. Its website has links to:

- resources to help manage incontinence, such as pelvic floor safe exercises, information on continence aids and financial assistance, bladder/bowel diaries, surgical options, the roles of health professionals including nurses and physiotherapists, a national public toilets map, leaflets designed specifically for indigenous people, and other information for carers and health professionals
- an online support forum for sharing information and ideas
- Bridge magazine, free for consumers
- the Australian Continence Exchange resources for health professionals at www.continencexchange.org.au

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• the Continence Aids Payment Scheme (CAPS), a government payment to help eligible people with permanent and severe incontinence purchase incontinence products from suppliers.

The Foundation is supported by the Department of Health's National Continence Program.

#### Contacts

National Continence Helpline	1800 33 00 66 freecall
	Mon-Fri 8am-8pm AEST
	helpline@continence.org.au
Website	www.continence.org.au
Email	info@continence.org.au
National office	Level 1, 30–32 Sydney Road
	Brunswick VIC 3056
Phone	(03) 9347 2522

ARTICLE

# Sodium-glucose co-transporter inhibitors

#### **Tilenka Thynne**

Clinical pharmacology registrar Department of Clinical Pharmacology Royal Adelaide Hospital

#### Matthew Doogue

Clinical pharmacologist Department of Medicine University of Otago Christchurch New Zealand

#### Key words

canagliflozin, dapagliflozin, diabetes mellitus type 2, hypoglycaemic drugs, kidney

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#### **SUMMARY**

Sodium-glucose co-transporter 2 inhibitors are a new class of drug for the treatment of type 2 diabetes. They lower plasma glucose concentrations by increasing renal excretion of glucose.

This class of drugs reduces glucose reabsorption in the kidney and lowers plasma glucose independent of changes in insulin concentrations or peripheral insulin resistance. They have a low risk of hypoglycaemia when used as monotherapy.

The known adverse effects of the sodiumglucose co-transporter 2 inhibitors are related to their mechanism of action. They include an increased risk of dehydration and genital and urinary tract infections because of the increase in urinary glucose.

#### Introduction

Current treatment options for type 2 diabetes focus on reducing insulin resistance, enhancing insulin secretion or providing exogenous insulin. However, the kidneys play an important role in glucose homeostasis. Increasing the excretion of glucose could lower blood glucose. This can be achieved by inhibiting the sodium-glucose co-transporter (SGLT).

# Physiology of renal glucose reabsorption

At normal concentrations of plasma glucose, the kidneys actively reabsorb almost all filtered glucose (approximately 180 g/day) with less than 1% excreted in the urine.<sup>1</sup> Glycosuria occurs when plasma glucose concentrations exceed the glucose reabsorbing capacity of the proximal tubules. This renal threshold for glucose is about 11 mmol/L.

Glucose is a hydrophilic molecule which needs to be transported across cell membranes to enter cells. Glucose transport can either be facilitative or active. Facilitative transport is driven by the concentration gradient across the cell membrane. Active transport is driven by sodium co-transport. Uptake of glucose in the intestine and kidneys is by active transport, mediated by members of the SGLT family. SGLT1 and SGLT2 are responsible for glucose reabsorption in the proximal tubules of the kidneys (Fig. 1).<sup>2</sup>

SGLT2 is a low-affinity, high capacity glucose transporter located in segment 1 of the proximal tubule (in the apical membrane of the tubule cells). Under normal circumstances SGLT2 reabsorbs about 90% of the filtered glucose (Fig. 2). SGLT2 is minimally expressed in other tissues.<sup>3</sup>

SGLT1 is a high-affinity, low capacity glucose transporter predominantly found in enterocytes of the small intestine where it transports glucose and galactose from the gut lumen across the gut wall. In the kidney SGLT1 is located in segments 2–3 of the proximal tubule. Following glucose reabsorption by SGLT2 early in the proximal tubule the remaining 10% of filtered glucose is reabsorbed by SGLT1 later in the proximal tubule.

#### SGLT2 as a therapeutic target

Familial renal glycosuria is a rare renal tubular disorder caused by a mutation in the SLC5A2 gene which encodes for SGLT2. It is characterised by persistent glycosuria with urinary glucose excretion up to 100 g/day in the absence of hyperglycaemia.<sup>4</sup> Familial renal glycosuria therefore acts as a model for therapeutic SGLT2 inhibition and, reassuringly, it is a benign condition. Despite chronic glycosuria, it is not associated with chronic kidney disease or urinary tract infections.

Phlorizin, a glucoside isolated from the bark of apple trees in the 19th century, was recognised in the 1950s as an inhibitor of glucose uptake by erythrocytes and of glucose transport in the kidneys and small intestine. In the 1990s phlorizin was shown to inhibit SGLT1 and SGLT2.<sup>5</sup> Further development of phlorizin was limited by its low bioavailability, lack of specificity and its adverse effects.

#### Pharmacology of SGLT2 inhibitors

The first two SGLT2 inhibitors approved in Australia, dapagliflozin and canagliflozin, have high bioavailability. They have a half-life of about 12 hours and are taken once a day. Dapagliflozin can be taken with or without food, while it is recommended that canagliflozin is taken before the first meal of the day. Both drugs are highly protein bound in plasma and are metabolised in the liver via glucuronidation. With these characteristics there is a low propensity for pharmacokinetic drug-drug interactions. However, inducers of glucuronidation can cause a modest increase in the metabolism of SGLT2 inhibitors. When inducers of glucuronidation (e.g. rifampicin, phenytoin or ritonavir) are prescribed, the product information for canagliflozin recommends a higher dose of 300 mg daily (usual starting dose 100 mg daily) or using an alternative blood glucose-lowering drug. The product information for dapagliflozin does not recommend a dose increase. Inhibition of metabolism by other glucuronidated drugs, for example mefenamic acid, is possible.<sup>6</sup> The clinical significance of these potential interactions with either drug is likely to be low. Canagliflozin may increase the plasma concentration of digoxin so digoxin concentrations should be monitored when starting or stopping canagliflozin.

Pharmacodynamic drug interactions may occur with thiazides and loop diuretics, increasing diuresis and the risk of dehydration. Changes in renal tubular handling of potassium associated with SGLT2 inhibition may be significant in patients at higher risk of hyperkalaemia, for example those with baseline renal impairment, taking ACE inhibitors or taking potassium-sparing diuretics.

In patients with mild to moderate liver impairment, no significant increase in drug concentrations was seen with either drug. A lower starting dose of dapagliflozin (5 mg) is recommended in patients with severe liver disease. There are no published data for canagliflozin in severe liver disease.

#### Caution in renal impairment

The efficacy of SGLT2 inhibitors is dependent on:

- glomerular filtration sufficient to deliver a glucose load to the proximal tubule
- sufficient drug reaching the proximal tubule.

SGLT2 inhibitors are therefore ineffective, and consequently not recommended, in moderate to severe renal impairment (estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m<sup>2</sup> or dialysis). There is limited experience in patients with eGFRs of 45–60 mL/min/1.73 m<sup>2</sup>.

Concerns about the long-term renal effects of chronic inhibition of tubular glucose uptake have been raised. However, familial renal glycosuria is not associated with increased renal impairment, and in short-term trials SGLT2 inhibitors have not been associated with a decline in renal function.<sup>7</sup> At this stage monitoring renal function at least annually is recommended and long-term studies are awaited.

#### SGLT2 inhibitors in type 2 diabetes

Treatment with an SGLT2 inhibitor causes dosedependent urinary net glucose losses of 20–70 g

# *Fig.* 1 Location of SGLT1 and SGLT2 in the proximal tubules of the kidney



#### Fig. 2 Action of SGLT2 in the proximal tubule

#### A Normal function



#### B SGLT2 inhibited



EXPERIMENTAL AND CLINICAL PHARMACOLOGY

SGLT inhibitors - mechanisms of action

per day. This varies with the degree of hyperglycaemia. The US Food and Drug Administration analyses of clinical trials found dapagliflozin reduces glycated haemoglobin (HbA1c) in patients with type 2 diabetes by 4-9 mmol/mol (0.4-0.8%), depending on the initial HbA1c.8 Similarly for canagliflozin there was a dosedependent HbA1c reduction of 4-11 mmol/mol (0.4-1%).9 This is comparable to the effect of dipeptidyl peptidase 4 inhibitors, but less than that of metformin, sulfonylureas or glucagon-like peptide-1 analogues.<sup>10</sup> The reduction in blood glucose concentrations occurs independently of any increase in insulin concentrations or decrease in peripheral insulin resistance. In addition the glycosuria causes a caloric loss, which has been associated with an average weight loss of 2-3 kg over 6-12 months in clinical trials.<sup>11</sup>

#### Mechanisms of potential harms

The mechanism of action of the SGLT2 inhibitors explains some of their reported adverse effects. The risk of hypoglycaemia is low when used as monotherapy or in combination with metformin. However, the risk of hypoglycaemia increases when SGLT2 inhibitors are combined with insulin or sulfonylureas.<sup>11</sup>

The glycosuria is accompanied by a small increase in urinary volume of about 100–500 mL/day due to osmotic diuresis. The consequent intravascular depletion may contribute to a small but consistent drop in blood pressure and a modest increase in postural hypotension.

The SGLT2 inhibitors are associated with a small increase in the rates of both genital infections and

urinary tract infections. This may be a consequence of induced glycosuria.

There are concerns about SGLT2 inhibition and bone health because of changes in the renal tubular handling of calcium, magnesium and phosphate, and preclinical reports of hyperostosis in rats. Calcium excretion can increase, but short-term studies (up to 24 weeks) have not shown a decline in bone mineral density with either drug compared to controls.<sup>9,12</sup> Mild elevations of parathyroid hormone have been observed<sup>9,13</sup> and the long-term safety of these drugs in regard to bone health and fracture risk is unclear.

There have also been concerns raised about a possible increase in the incidence of bladder and breast cancer. Continued surveillance for breast and bladder cancer with dapagliflozin, canagliflozin and future SGLT2 inhibitors will be required.

There are SGLT transporters in other tissues. Antagonism of these transporters may have long-term harmful or beneficial effects not detected by shortterm studies.

#### Conclusion

SGLT2 inhibitors are a new class of drugs for lowering plasma glucose. They reduce the renal reabsorption of urinary glucose. The reduction in plasma glucose is independent of insulin secretion and insulin peripheral resistance. The long-term effects of SGLT2 inhibitors are unknown.

Conflict of interest: none declared

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SELF-TEST

True or false?

kidney.

**QUESTIONS** 

5. Sodium-glucose

co-transporter 1 is

mainly found in the

6. Inhibition of the

Answers on page 35

co-transporter reduces

sodium-glucose

urine volume.

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16 Full text free online at www.australianprescriber.com

# Sodium-glucose co-transporter inhibitors

#### **Clinical applications**

#### SUMMARY

Inhibition of the sodium-glucose co-transporter 2 in the kidney lowers blood glucose by increasing glucose excretion in the urine. The associated osmotic diuresis and urinary loss of sodium reduces blood pressure.

Canagliflozin and dapagliflozin are sodium-glucose co-transporter 2 inhibitors that have been studied as monotherapy and in combination with other drugs for type 2 diabetes. They reduce concentrations of glycated haemoglobin by 6–9 mmol/mol (0.5–0.8%) more than placebo.

Patients may lose 2–3 kg during treatment. Hypoglycaemia is more likely to occur if a sodium-glucose co-transporter 2 inhibitor is used in combination with other drugs that lower blood glucose. Low density lipoprotein cholesterol increases during treatment.

Glycosuria increases the risk of genitourinary infections. Increased calcium excretion could potentially reduce bone density.

Long-term studies are investigating the cardiovascular safety of these drugs. These studies could also yield data about a possible increased risk of malignancy.

#### Introduction

The currently available oral therapies for type 2 diabetes all have limitations which mean that patients' therapeutic goals<sup>1</sup> may not be easily and safely achieved, even when combinations of drugs are prescribed. New blood glucose-lowering therapies that are effective and well tolerated are needed.

The role of the kidney in the maintenance of blood glucose has been relatively overlooked. It is now the target of the sodium-glucose co-transporter (SGLT) inhibitors.

#### **Renal glucose homeostasis**

The kidney has an important role in glucose homeostasis through gluconeogenesis and reabsorption of filtered glucose. In healthy adults, approximately 180 g/day of glucose is filtered at the glomerulus and virtually all is reabsorbed by SGLTs.<sup>2</sup>

Drugs which inhibit the co-transporters increase glucose excretion and treat diabetes in a different way from other therapies. The associated natriuresis may also reduce blood pressure.

Many co-transporter inhibitors are in various stages of clinical development. Of greatest contemporary relevance to Australian prescribers are dapagliflozin and canagliflozin. Others in at least phase II development are empagliflozin, ertugliflozin and ipragliflozin.

#### **Clinical effects**

An aim of treatment for type 2 diabetes is to optimise glycaemic control (and thus reduce the risk of chronic complications) without inducing hypoglycaemia, weight gain or other adverse effects. SGLT2 inhibitors reduce the plasma glucose concentration without stimulating insulin release. Hypoglycaemia should thus be a risk only when these drugs are given with an insulin secretagogue (a sulfonylurea) or insulin. The loss of calories through glycosuria means that SGLT2 inhibitors promote weight loss.

#### Glycaemic control

The glycaemic efficacy of dapagliflozin has been studied in several thousand patients in a range of trials as monotherapy and in combination with other oral drugs or insulin. At its recommended dose of 10 mg daily, dapagliflozin produces placebo-adjusted mean reductions of 6-9 mmol/mol (0.5-0.8%) in glycated haemoglobin (HbA1c) from initial concentrations of 7.5% or over, when given for at least three months.<sup>3</sup> These effects are similar whether the drug is given as monotherapy, in initial combination with metformin, or as add-on therapy to metformin, a sulfonylurea, a thiazolidinedione or insulin. As with other oral therapies for type 2 diabetes, the greatest mean reductions (>1%) are in patients with the highest pre-treatment HbA1c (>75 mmol/mol (>9%)). There is also a fall in mean fasting plasma glucose of at least 1 mmol/L. These results are broadly similar to those in comparable studies of other oral drugs for lowering blood glucose.<sup>4</sup> There is evidence from add-on studies with two-year follow-up that the glycaemic effect of dapagliflozin is sustained.5

#### **Timothy Davis**

Winthrop Professor School of Medicine and Pharmacology University of Western Australia Fremantle Hospital Western Australia

#### Key words

canagliflozin, dapagliflozin, diabetes mellitus type 2, urinary tract infection

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SGLT inhibitors - clinical applications

Dapagliflozin appears ineffective in patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m<sup>2</sup>. It has not been adequately assessed in patients aged 75 years or over and so is not currently recommended for use in this age group.

Canagliflozin 300 mg daily appeared to have similar efficacy to dapagliflozin in a similar range of phase III studies ranging from monotherapy to add-on therapy with other oral drugs and insulin.<sup>6</sup> It is possible, however, that the lower specificity for SGLT2 relative to SGLT1 might mean that canagliflozin has greater (SGLT1-associated) renal and gastrointestinal glucose losses than dapagliflozin. Such a hypothesis needs to be addressed in head-to-head studies which also consider relative tolerability and safety.

In contrast to studies of dapagliflozin in renal impairment which have not shown a statistically significant glycaemic effect, canagliflozin led to a significant mean reduction of 0.4% in HbA1c over placebo in patients with an eGFR of 30–50 mL/min/ 1.73 m<sup>2,7</sup>

#### Weight

Dapagliflozin causes weight loss (typically 2–3 kg and mostly visceral fat) in the first 2–3 months which then plateaus. Canagliflozin has a similar effect.

#### Blood pressure

In phase III studies both dapagliflozin and canagliflozin are associated with a significant mean reduction in systolic blood pressure of 1–6 mmHg more than placebo.<sup>3,6</sup> This change in systolic pressure is more than expected from weight loss and mild dehydration (haematocrit typically increases 1–3%). It reflects the osmotic diuresis and natriuresis associated with the mechanism of action of these drugs. The concomitant drug-related reductions in diastolic blood pressure are smaller than the systolic changes, but are still statistically significant. There is no attenuation of blood pressure effects in the case of canagliflozin given to patients with an eGFR of30–50 mL/min/1.73 m<sup>2</sup>.<sup>7</sup>

#### **Adverse effects**

In clinical trials of dapagliflozin, 3.2% of patients discontinued because of adverse events. These included genitourinary infections and raised serum creatinine.

#### Cardiovascular safety

The incidence of clinical events related to intravascular volume depletion (such as symptomatic postural hypotension and dehydration) was approximately double for dapagliflozin compared with placebo or comparator drugs in phase III studies.<sup>3</sup> There was a similar result for canagliflozin.<sup>6</sup> With both drugs, there was no significant excess of severe events associated

with their use, and discontinuations due to polyuria, nocturia or dehydration were rare. In the case of canagliflozin, a reduction in intravascular volume was most evident when the drug was taken by patients with an eGFR less than 60 mL/min/1.73 m<sup>2</sup>, who were aged 75 years or over, or taking loop diuretics. In these patient groups it is recommended that therapy begins with 100 mg rather than 300 mg daily.

Dapagliflozin<sup>3</sup> and especially canagliflozin<sup>6</sup> increase serum low density lipoprotein cholesterol (placeboadjusted changes 4.6% and 8.2% respectively). A meta-analysis of 14 clinical studies of dapagliflozin did not show an increase in macrovascular disease,<sup>3</sup> but longer-term studies are needed to detect whether the risk of atherosclerosis is increased. However, in a similar meta-analysis<sup>6</sup> there was a transient excess of cardiovascular events (mainly stroke) in the first month of treatment with canagliflozin. This did not appear to be related to clinically evident reductions in intravascular volume that might facilitate thrombosis. This analysis included events from the long-term cardiovascular safety trial Canagliflozin Cardiovascular Assessment Study (CANVAS) which is ongoing. A postmarketing cardiovascular safety trial of dapagliflozin (DECLARE-TIMI58) that is designed to last up to six years is also in progress.

#### Renal function and genitourinary infections

In studies of dapagliflozin<sup>3</sup> and canagliflozin<sup>6</sup>, there have been small reversible falls in the eGFR. These were greatest (around 10%) in patients with moderate renal impairment.

Monitoring of renal function is recommended before starting an SGLT2 inhibitor and at least yearly thereafter. Renal function should be checked before and periodically after starting other drugs that may influence renal function. More frequent monitoring (3–6 monthly) should be considered in patients with an eGFR approaching the level at which SGLT2 inhibition should be discontinued (60 mL/min/1.73 m<sup>2</sup> for dapagliflozin and 30 mL/min/1.73 m<sup>2</sup> for canagliflozin).

In patients with micro- or macroalbuminuria, canagliflozin is associated with an approximate 50% reduction in urinary albumin excretion. This is sustained for up to a year. Dapagliflozin does not appear to influence albuminuria.

There is a mildly increased risk of non-recurrent uncomplicated urinary tract infection with SGLT2 inhibitors,<sup>3,6</sup> especially in females and patients with a previous history of urinary tract infection. However, both dapagliflozin and canagliflozin increase the risk of genital fungal infections five-fold in both males and females. The most frequent are vulvovaginal infections (most commonly candidal) that respond

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to conventional antifungal drugs. However, because no data on prevalence of circumcision have been reported in phase III studies, the relative risk of balanoposthitis in uncircumcised men may be much greater than vulvovaginal infections in women.

#### Cancer

In clinical studies of dapagliflozin there was an imbalance in the numbers of cases of cancer. The excess of bladder, breast and prostate malignancies<sup>3</sup> contributed to the drug's rejection by the US Food and Drug Administration (FDA).<sup>8</sup> The manufacturers are, however, continuing surveillance to determine whether the imbalance is due to the play of chance or a true drug-related adverse effect. There was no apparent increase in the risk of malignancy in pre-clinical and clinical studies of canagliflozin.<sup>6</sup>

#### Bone health

Canagliflozin and dapagliflozin cause mildly increased calcium excretion with consequent secondary hyperparathyroidism – effects which may be transient.<sup>3,8</sup> This is mechanistically similar to the action of loop diuretics which increase urinary calcium in parallel with sodium excretion and are recognised risk factors for osteoporosis. There have been no reports of renal calculi during SGLT2 inhibitor treatment.

Bone density data for dapagliflozin over one year did not show a significant change at any site, but canagliflozin studies showed a small decrease which was attributed to the effects of weight loss. There was, however, a greater number of fractures with canagliflozin compared with comparator drugs. This led the FDA to mandate a bone safety study as part of a postmarketing pharmacovigilance program.<sup>7</sup>

#### Other concerns

Hepatic impairment reduces glucuronidation and so increases dapagliflozin exposure. There are no clinically meaningful interactions with drugs likely to be prescribed with canagliflozin and dapagliflozin, although changes in renal function associated with their use may need to be considered in relation to renally excreted co-prescribed drugs such as metformin.

There is no evidence that canagliflozin and dapagliflozin are associated with hepatotoxicity, but neither is recommended for patients with severe hepatic impairment.<sup>3,6</sup> The long-term cardiovascular safety studies should provide data on liver function abnormalities and other potential end points of interest flagged by the FDA. These include malignancies, pancreatitis, hypersensitivity and photosensitivity reactions, fractures and adverse pregnancy outcomes.<sup>9</sup> Studies in children with diabetes are also needed.

#### Likely place in therapy

The current Australian indications for dapagliflozin in patients with type 2 diabetes managed with an appropriate diet and exercise regimen are:

- monotherapy when metformin is contraindicated or not tolerated
- initial combination therapy with metformin when metformin monotherapy is unlikely to achieve adequate glycaemic control (such as when the initial HbA1c is very high)
- add-on combination with metformin or a sulfonylurea when these drugs alone do not provide adequate glycaemic control
- add-on combination with insulin (alone or with one or both of metformin or a sulfonylurea) when these regimens do not provide adequate glycaemic control.

Canagliflozin has a similar range of indications, but with less restrictions than dapagliflozin based on renal function and age.

Blood glucose-lowering therapies that are associated with weight loss are understandably attractive to the majority of patients with type 2 diabetes who are either overweight or obese. The only other therapies with this property are metformin and especially the glucagon-like peptide 1 (GLP1) analogue class that includes exenatide and liraglutide. These analogues are injectable therapies and they can cause significant gastrointestinal symptoms, primarily nausea. However, they appear to have a more durable effect on body weight and are more potent blood glucose-lowering therapies than the SGLT2 inhibitors.

Given the cost of new diabetes therapies, and the long-term experience with metformin and sulfonylurea drugs, SGLT2 inhibitors could be an alternative to incretin-based therapies (dipeptidyl peptidase inhibitors or GLP1 analogues) in combination with either metformin or a sulfonylurea when one or other of these drugs is contraindicated or not tolerated. However, their mode of action suggests they may be a useful adjunct to more established therapies, including potential use in type 1 diabetes.

#### Conclusion

The inhibitors of the sodium-glucose co-transporter improve glycaemic control with a low incidence of hypoglycaemia and have beneficial effects on body weight and blood pressure. They have the convenience of once-daily dosing and their mechanism of action means that they can be combined safely with other oral glucose-lowering drugs and insulin.

#### EXPERIMENTAL AND CLINICAL PHARMACOLOGY

SELF-TEST

True or false?

cholesterol.

8. An inhibitor of the sodium-glucose

**QUESTIONS** 

7. Canagliflozin and

dapagliflozin increase low density lipoprotein

co-transporter should not be combined with

insulin because of the

risk of hypoglycaemia.

Answers on page 35

#### SGLT inhibitors - clinical applications

Their main adverse effects are increases in genitourinary infections, dehydration-related symptoms including postural hypotension, and raised serum low density lipoprotein cholesterol. Ongoing surveillance including large-scale cardiovascular safety trials should provide objective data on the possible increased risk of stroke, fracture and malignancy. Timothy Davis has served on Australian diabetes advisory boards which have considered dapagliflozin (Bristol-Myers Squibb, AstraZeneca), canagliflozin (Johnson & Johnson), empagliflozin (Boehringer Ingelheim) and ertugliflozin (Merck Sharp and Dohme, Pfizer). He has received speaker's fees and sponsorship to attend meetings from Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim and Merck Sharp and Dohme, and research funding from Merck Sharp and Dohme.

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# Medicines Safety Update



Australian Government

**Department of Health** Therapeutic Goods Administration

Volume 5, Number 1, February 2014

#### In this issue

- Quetiapine and QT prolongation
- bioCSL Fluvax not for children under 5 years
- How you can play a vital role in medicine regulation

# Quetiapine and QT prolongation

Health professionals are advised that the Product Information for quetiapine has been updated to include additional information regarding risks of QT prolongation.

Postmarketing reports of QT prolongation associated with quetiapine treatment have occurred not only in the context of overdose, but also with concomitant illness and in patients taking other drugs known to cause electrolyte imbalances or increase the QT interval. Quetiapine, which is marketed as Seroguel and multiple generics, is an atypical antipsychotic drug indicated for the treatment of schizophrenia and bipolar disorder. TGA investigations found that, while the Australian Product Information (PI) had a precaution for use with cardiovascular disease, family history of QT prolongation, congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia and hypomagnesaemia, it did not specifically state the need to avoid use in circumstances that may increase the occurrence of torsades de pointes and/or sudden death.

#### New information

The PI for quetiapine products now advises, particularly in elderly patients, to avoid concomitant treatment with antipsychotics and other drugs that are known to prolong the QT interval. These include:

- Class IA antiarrhythmics (such as disopyramide)
- Class III antiarrhythmics (such as amiodarone and sotalol)
- antipsychotics (such as ziprasidone, chlorpromazine and haloperidol)
- antibiotics (such as erythromycin)
- others (such as citalopram, pentamidine and methadone).

The updated information also advises that quetiapine should be avoided in circumstances that may increase the risk of torsades de pointes and/or sudden death, including a history of cardiac arrhythmias, hypokalaemia or hypomagnesaemia, and congenital prolongation of the QT interval.

Additionally, the PI has also been updated to include further information about the risk of:

- venous thromboembolism (VTE)
- akathisia
- neutropenia.

#### Adverse event reports in Australia

Over the 13 years that quetiapine has been registered in Australia, from March 2000 to August 2013, there have been a total of 807 adverse event reports made to the TGA relating to its use. Of those reports, 23 involved QT prolongation. More than half involved concomitant drugs that can increase the QT interval.

There were two reports of cardiac arrest in which QT prolongation was also noted, and another report of fatal cardiac arrest in which QT prolongation was not reported. Meanwhile there was one report of torsades de pointes, associated with hypokalaemia and hypomagnesaemia.

#### Information for health professionals

Health professionals are encouraged to review the latest PI for quetiapine and particularly the updated information regarding QT prolongation, VTE, akathisia and neutropenia in the precautions section.

Quetiapine treatment in combination with antipsychotics and other drugs that are known to prolong the QT interval should be avoided, particularly in elderly patients. Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)



# bioCSL Fluvax – not for children under 5 years

Despite a range of actions taken in 2013 to ensure the safe use of seasonal influenza vaccines in children, there were still 43 confirmed cases of bioCSL Fluvax being administered to children under 5 years of age last year.

Health professionals are reminded that bioCSL Fluvax is registered for use in children from the age of 5 years and should not be used in children under 5 years of age. Additionally, bioCSL Fluvax should only be used in children aged 5 to under 9 years based on careful consideration of potential benefits and risks in the individual child. This information is reinforced in the black box warning (Fig. 1) in the Product Information.

During the 2010 influenza season, an excess number of febrile reactions and febrile convulsions occurred in children under 5 years of age after immunisation with bioCSL Fluvax. As a result, the approved indication for bioCSL Fluvax was changed.

The TGA also advises health professionals to avoid using 'Fluvax' as a generic term for influenza vaccine to minimise the potential for confusion.

#### bioCSL Fluvax safety initiatives

While some errors are still occurring, actions taken to ensure the safe use of bioCSL Fluvax in children have been effective in significantly reducing the number of cases of incorrect administration. In 2013, there were 43 confirmed cases of children under 5 years of age being given bioCSL Fluvax out of 48 361 influenza vaccines recorded on the Australian Childhood Immunisation Register in this same age group. This compares to 115 confirmed reports in 2012. Safety initiatives undertaken during 2013 included:

 communication activities by the Commonwealth and State and Territory health departments regarding bioCSL Fluvax and other influenza vaccines that can be used in children, as well as the need to report adverse events for all ages

#### Figure 1 Black box warning in bioCSL Fluvax Product Information

WARNING: This season's vaccine is indicated for use only in persons aged 5 years and over. It must not be used in children under 5 years (see Contraindications). It should only be used in children aged 5 to under 9 years based on a careful consideration of potential risks and benefits in the individual (see Precautions).

- communication activities by bioCSL, including a medical communications campaign following market research into provider practices
- changes to packaging for bioCSL Fluvax, including a warning on the outer packaging, syringes and syringe wraps, and development of a vaccine refrigerator sticker (Fig. 2)
- direct follow-up by State and Territory public health units of general practitioners who were noted as having administered bioCSL Fluvax to children under 5 years of age during the year.

The TGA received no reports of adverse events involving the administration of bioCSL Fluvax to a child under 5 years of age during 2013. Similarly, no additional safety concerns were detected by two enhanced influenza adverse events surveillance projects funded by the Department of Health.

#### Actions for 2014

In addition to actions taken in 2013, this year bioCSL Fluvax will have warnings on both sides of the packaging and a safety message will be included in the Influenza Specialist Group communication materials. Online learning tools for immunisation providers are also being developed by bioCSL.

Figure 2

bioCSL Fluvax packaging warning and the vaccine refrigerator sticker

### DO NOT USE IN CHILDREN UNDER 5 YEARS



# How you can play a vital role in medicine regulation

The TGA draws on the expertise of highly qualified health professionals from around Australia to help it regulate medicines and other therapeutic goods.

Health professionals with a broad range of skills and experience are appointed to the TGA's various statutory advisory committees. They provide independent advice regarding medicines, vaccines, biologicals and medical devices.

One such expert advisory committee is the Advisory Committee on the Safety of Medicines (ACSOM).

This committee serves to advise and make recommendations to the TGA on:

- the safety of medicines
- the risk assessment and risk management of medicines.

The ACSOM may also provide advice to the TGA on

other matters related to the detection, assessment, understanding and prevention of adverse events, and any other matters referred to it.

A major role for this committee is to provide advice on the quality and appropriateness of Risk Management Plans for high-risk medicines (such as those from a new class), which are designed to define and proactively manage risks relating to a medicine over its entire lifecycle.

The TGA regularly seeks expressions of interest from people interested in joining expert advisory committees. By serving as a member of one of these committees, you can help the TGA to effectively regulate increasingly complex therapeutic goods to protect the continuing health and safety of all Australians.

For further information visit the TGA website www.tga.gov.au.



#### 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
- **by fax** to (02) 6232 8392
- by email to ADR.Reports@tga.gov.au

For more information about reporting, visit 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

For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114

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 Claire Behm

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### Medicinal mishap Intravenous paracetamol in paediatrics: cause for caution

#### **Madlen Gazarian**

Consultant in Paediatric Clinical Pharmacology and Therapeutics Member Editorial Committee<sup>1</sup>

Honorary Associate Professor<sup>2</sup>

#### **Anna Drew**

Quality Use of Medicines Project officer<sup>1</sup>

**Alexandra Bennett** Co-Executive Officer<sup>1</sup>

<sup>1</sup> NSW Therapeutic Advisory Group <sup>2</sup> University of NSW Sydney

#### Case 1

A two-week-old 2.9 kg baby presented to a general hospital emergency department with acute bowel obstruction and underwent urgent laparotomy. Postoperatively the baby was given three doses of 290 mg intravenous paracetamol (instead of the prescribed 29 mg dose) over a 38-hour period. The error was detected 1–2 hours after the third dose, which was initially thought to be a single overdose. The preceding two overdoses were discovered six hours later and N-acetylcysteine was given, following the advice of a Poisons Information Centre toxicologist. The baby remained clinically stable and liver transaminases were normal throughout.

#### Case 2

A 5.65 kg infant admitted to a general hospital was prescribed '80 mg paracetamol IV/PO/PR'. Poor legibility of the prescription led to interpretation of the dose as 280 mg. A 1000 mg vial of intravenous paracetamol was connected to an infusion pump set at 168 mL/hr for 10 minutes. The infusion continued beyond the intended duration and a total dose of 430 mg (75 mg/kg) was given.

#### Comment

Paracetamol has a good safety record when used appropriately. Since intravenous paracetamol became widely available there have been multiple inadvertent 10-fold overdoses in infants.<sup>1,2</sup> A key contributing factor is the 10 mg/mL strength of intravenous paracetamol – health professionals mix up the mg and the mL dose. Ten-fold dosing errors occur regularly in paediatric patients and are a recognised source of significant harm, including deaths. A recent review examines contributing factors and recommends general strategies for harm prevention.<sup>3</sup>

The NSW Therapeutic Advisory Group (NSW TAG) has developed comprehensive, evidence-based guidance on the appropriate and safe use of intravenous paracetamol.<sup>1</sup> There are key recommendations for clinicians caring for paediatric patients in all hospital settings. Importantly, NSW TAG's guidance provides an up-to-date dose recommendation for intravenous paracetamol in infants; this differs from the current Australian product information for infants weighing less than 10 kg. The justification for this 'off-label' dose recommendation is discussed. NSW TAG's guidance also includes advice about using paracetamol for fever in adults with stroke, dosing in underweight adults and frail older people, and more general advice for preventing hepatotoxicity in adults.

#### **Recommendations**<sup>1</sup>

- Reserve intravenous paracetamol for acute, shortterm treatment of mild-moderate pain when enteral administration is not possible.
- Undertake a comprehensive risk assessment before treatment and review daily – exercise particular caution in infants less than six months of age. General risk factors for paracetamol hepatotoxicity in paediatric patients (see Box) and for underweight adults and frail older people less than 50 kg are described in relevant sections of NSW TAG's guidance.
- Follow general principles for safe paediatric prescribing,<sup>4</sup> including:
  - always write legibly printing in capitals is strongly recommended
  - check the basis for the dose calculation in a current paediatric prescribing reference or other up-to-date, evidence-based medicines information resource
  - calculate the dose using the patient's current, accurate (or, for overweight children, ideal) body weight (advice on how to estimate ideal body weight using paediatric growth charts is provided in the guidance)
  - independently double check the calculated dose (using a calculator) at the time of prescribing and at each administration

#### Box Key risk factors for paracetamol hepatotoxicity \*

febrile illness	
younger age	
prolonged fasting	
vomiting or dehydration	
chronic undernutrition	
severe hepatic impairment	

\* adapted from reference 1

- prescribe the dose in milligram (mg) units.
   Additional specification of the volume in millilitres (mL) and the strength of the solution may maximise the clarity of the intended dose for liquid medicines, but the primary order should always be expressed in dose units.
- Specify only one route of administration, as the appropriate dosing interval and recommended maximum daily dose differs for each administration route. Prescribing 'paracetamol IV/PO/PR' is inappropriate and unsafe.
- In small infants, the volume containing the required dose should be drawn up in a syringe (using a 5 or 10 mL syringe for infants less than 10 kg), diluted appropriately and administered using computerised infusion control.
- Ensure no other formulations of paracetamol are concurrently prescribed or administered and the

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safe maximum daily dose (from all sources) is not exceeded.

- When prescribing 'paracetamol IV', specify the brand name in addition to the generic name to avoid confusion with other formulations.
- All health professionals prescribing and administering intravenous paracetamol for paediatric patients should be appropriately educated in the general principles of safe paediatric prescribing and medicines use as well as in the appropriate and safe use of intravenous paracetamol specifically.

#### Conflict of interest: none declared

Acknowledgements: Thanks to Jared Brown, Senior Poisons Specialist, and Dr Naren Gunja, Medical Director, NSW Poisons Information Centre, for their help with case identification. The valuable contribution of the NSW TAG Paracetamol Expert Advisory Group and the NSW TAG Editorial Committee to the development of NSW TAG's guidance document is also gratefully acknowledged.

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18 April 2014

### Book reviews AMH Children's Dosing Companion

#### **Yashwant Sinha**

Clinical research fellow Centre for Kidney Research The Children's Hospital at Westmead Sydney Australian Medicines Handbook; 2013. Electronic version (also available in print)

This Australian Medicines Handbook dosing companion is Australia's new national paediatric formulary, representing more than 10 years planning and development facilitated by the Australian Health Ministers' Advisory Council and the Paediatric Medicines Advisory Group. It aims to provide clear guidance for practitioners prescribing for children and to reduce variability in prescribing practices.

It provides dosing information for the most commonly used medicines in children in community and hospital practice, and includes neonates born at term up to children aged 18 years. It does not include dosing



guidelines for premature infants or some medicines used in hospitals such as anaesthetics, normal human

immunoglobulins and intravenous fluids.

This resource is for use on desktop computers, tablets and smartphones. It is arranged as an alphabetical list of drug monographs which may be searched using generic or brand names. Dosing guidelines are provided 'per indication' and 'per dose' with a maximum dose provided where possible. Sections outlining off-label use and practice points are included. There is a link to the Pharmaceutical Benefits Scheme (PBS), although all monographs include the statement 'PBS restrictions may not pertain to children'. This is a little confusing as many PBS-listed medicines are not restricted by age.

General guidelines include principles of prescribing for children, common paediatric prescribing errors, off-label prescribing and prescribing in special situations. The appendices include the Australian Immunisation Handbook vaccination schedule and some useful algorithms for body surface area, resuscitation, topical corticosteroids and intraosseous injection technique. Lists of contact details for pharmaceutical companies and drug information centres in each state are provided.

Overall, the companion provides accurate, useful information to assist practitioners prescribing for children. It is of greatest practical value for children in the community, however the need for a paid subscription may limit uptake by prescribers. Use within tertiary paediatric settings would require a more complete list of medicines.

#### Ethics and law for the health professions. 4th ed.

Kerridge I, Lowe M, Stewart C.

#### **Paul A Komesaroff**

Professor of Medicine Monash Centre for Ethics in Medicine and Society Monash University Melbourne

#### Sydney: The Federation Press; 2013. 1232 pages

This book is an extraordinary undertaking that, against the odds, succeeds in providing a comprehensive, entertaining and readable introduction to the key issues in contemporary bioethical theory and law. It offers health professionals an impressive and valuable resource of almost breathtaking ambition and scope.

The first challenge the authors had to address in writing this work was how to define bioethics. This is a controversial issue because what constitutes the boundaries of the discipline is disputed, the possible list of topics and philosophical perspectives from which to consider them is very extensive and there are deep disagreements about the relationship between bioethics and law. In response to this uncertainty they have chosen the broadest possible approach, covering all the major extant philosophical theories, key concepts, areas of clinical practice and subjects raising ethical issues in research and public policy.

Familiar topics such as end-of-life issues, consent, competency, truth telling and confidentiality and privacy are well treated. Specific topics arising in relation to nursing, students, indigenous issues, children, the elderly and mental illness are usefully addressed, and there are extensive sections on ethical issues associated with new technologies, genetics and public and global health.

An especially welcome feature is the extension of the discussion to include contemporary debates about non-human animals and the environment. In all cases, the ethical and legal issues are discussed in a complementary manner, with clarity, precision and at times even humour. Indeed, the jargon-free style of presentation is one of the book's most striking attributes.

This is not to say that the book is without problems or limitations. The sheer size of the project makes it inevitable that many issues and philosophical theories are treated in a rudimentary, sometimes superficial, manner. This makes the discussion at times uneven, with some topics – such as consent and competency – being treated in authoritative detail in relation both to legal and ethical theory. Other topics – such as the presentation of some contemporary philosophical works – remain excessively brief and schematic.

It is possible that this may confuse and even frustrate some readers. However, it is always open to those who object to brief summaries of large and complex areas of thought to overcome the problem the hard way – by going back to the primary literature itself. Even here it can be argued that the mere provision of a summary and reading list will help facilitate access to unfamiliar, specialist areas of ethical and legal theory for many readers in the healthcare professions who would not otherwise come into contact with them.

Health workers new to bioethics will find this book a convenient and readable introduction, and those already familiar with the field will find it a useful, up-to-date guide to the rapidly expanding contemporary literature.

Paul Komesaroff is Chair of the Editorial Board of the Journal of Bioethical Inquiry



## New drugs: transparency

Access to the information collected during clinical trials is important for preparing the new drug comments in *Australian Prescriber*. A lot of this information is unpublished, but is used by the Therapeutic Goods Administration (TGA) when it evaluates new drugs. *Australian Prescriber* routinely asks pharmaceutical companies to provide a copy of the clinical evaluation data which support the safety and efficacy of their products. Few companies provide this level of transparency.

Almost 10 years ago *Australian Prescriber* started to publish a rating of the companies' cooperation. This was called the T-score (see box). While some companies are willing to provide data, others do not even respond to the request for information (see Table online at www.australianprescriber.com/ magazine/37/1/artid/1488).

In the last few years the TGA has started to publish information about what was considered when it evaluated a new drug for the Australian market. These Australian Public Assessment Reports (AusPARs) include information from the TGA's clinical evaluation. This then resulted in some companies, responding to requests for data, referring *Australian Prescriber* to the AusPAR rather than providing the data. As the AusPAR is a public document and does not contain the full clinical evaluation, the Editorial Executive Committee decided that companies which only provided an AusPAR would be given the minimum T-score. To be advised to read the AusPAR is particularly unhelpful if the AusPAR has not been published before the drug is launched onto the Australian market. The TGA is working to reduce this delay in publishing AusPARs. In addition, the TGA has been providing extracts of its evaluations, as attachments to the AusPARs, since July 2013.

The transparency of drug regulation is gradually improving, but *Australian Prescriber* will continue to monitor the willingness of the pharmaceutical industry to provide information about clinical trials of new drugs.

#### **T-scores**

X

X

- T T T manufacturer provided the clinical evaluation
   T T manufacturer provided additional useful information
   T manufacturer provided the AusPAR and/or the product information
  - manufacturer declined to supply data

manufacturer did not respond to request for data

# New drugs

#### Alogliptin

#### Approved indication: type 2 diabetes Nesina (Takeda) 6.25 mg, 12.5 mg and 25 mg tablets Australian Medicines Handbook section 10.1.3

Alogliptin is the fifth dipeptidyl peptidase 4 (DPP4) inhibitor to be approved for diabetes in Australia, along with linagliptin (Aust Prescr 2012;35:70-1), saxagliptin (Aust Prescr 2011;34:89-91), vildagliptin (Aust Prescr 2010;33:89-95) and sitagliptin (Aust Prescr 2008;31:49-55).

DPP4 enzymes inactivate incretin hormones which are produced after a meal. These hormones promote insulin release and lower glucagon production which leads to lower serum glucose concentrations. By inhibiting DPP4 enzymes, the 'gliptins' prolong the effects of incretins and improve glycaemic control (Aust Prescr 2008;31:102-4 and 104-8).

Alogliptin's bioavailability is 100%. Following oral administration, peak plasma concentrations are reached after 1–2 hours. The drug is not extensively metabolised and clinically relevant pharmacokinetic drug interactions are not expected. Alogliptin has a terminal half-life of 21 hours and the majority of the dose (60–71%) is eliminated unchanged in the urine.

Alogliptin has been investigated in numerous randomised controlled trials in patients whose type 2 diabetes was not adequately managed with diet and exercise or other antidiabetic drugs. Some of these trials are listed in the Table.

Once-daily alogliptin was found to significantly reduce glycated haemoglobin (HbA1c) – a surrogate marker for glycaemic control – when added to stable doses of metformin<sup>1</sup>, glibenclamide<sup>2</sup>, pioglitazone<sup>3</sup> or insulin (with or without metformin)<sup>4</sup>. HbA1c reductions were also seen when it was added to dual therapy with metformin and pioglitazone<sup>5</sup> (see Table).

As initial therapy, alogliptin was significantly better than placebo at lowering HbA1c.<sup>6</sup> It also showed benefit as initial therapy in combination with pioglitazone<sup>7</sup> (see Table).

During trials, the most common adverse event with alogliptin was pruritus. Headache, diarrhoea, myalgia, rash, musculoskeletal pain, abdominal pain, nausea and infections (influenza, nasopharyngitis, upper respiratory tract infection) were also common (1–10% of patients). Severe hypersensitivity reactions (e.g. angioedema, Stevens-Johnson syndrome), hepatic failure and pancreatitis have been reported in postmarketing surveillance. Alogliptin is not recommended in patients with severe hepatic impairment.

Hypoglycaemia can occur when alogliptin is added to insulin or a sulfonylurea so these drugs may need to be given at lower doses during combination therapy.

Alogliptin is a category B3 pregnancy drug. There are no data in humans so it is best avoided during pregnancy. Alogliptin was excreted in breast milk in animal studies so there is a risk of exposure to a breastfeeding infant.

Renal function should be assessed before patients start alogliptin. Dose reduction is recommended in patients with moderate (creatinine clearance 30 to 50 mL/min) or severe renal impairment (creatinine clearance <30 mL/min) and those with end-stage renal disease requiring dialysis. Experience in patients with severe renal disease is limited and caution is urged.

As with other DPP4 inhibitors, alogliptin is modestly effective at lowering HbA1c. It provides another option for monotherapy or as an add-on therapy when a patient's diabetes is not controlled by metformin, a sulfonylurea, a thiazolidinedione or insulin. It can also be added as a third option in patients already taking metformin and pioglitazone. Despite showing benefit in trials, alogliptin is currently not indicated for initial combination therapy in Australia.<sup>7</sup>

**T** manufacturer provided additional useful information

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Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

#### Table Clinical trials of alogliptin in type 2 diabetes

Trials	Treatment arms	Mean baseline HbA1c (%)	Mean change in HbA1c (%) from baseline
Add-on studies			
Alogliptin plus metformin <sup>1</sup>	alogliptin 12.5 mg + metformin	7.9-8.0	-0.60
for 26 weeks	alogliptin 25 mg + metformin		-0.60
(527 patients)	placebo + metformin		-0.10
Alogliptin plus a sulfonylurea <sup>2</sup>	alogliptin 12.5 mg + glibenclamide	8.08	-0.39
for 26 weeks	alogliptin 25 mg + glibenclamide	8.09	-0.53
(JOO patients)	placebo + glibenclamide	8.15	+0.01
Alogliptin plus a thiazolidinedione <sup>3</sup>	alogliptin 12.5 mg + pioglitazone	8.1	-0.66
(metformin or a sulfonylurea allowed)	alogliptin 25 mg + pioglitazone	8.0	-0.80
(493 patients)	placebo + pioglitazone	8.0	-0.19
Alogliptin plus insulin <sup>4</sup>	alogliptin 12.5 mg + insulin	9.3	-0.63
(with or without metformin)	alogliptin 25 mg + insulin		-0.71
(390 patients)	placebo + insulin		-0.13
Alogliptin plus metformin and a thiazolidinedione <sup>5</sup>	alogliptin 25 mg + metformin + pioglitazone 30 mg	8.3	-0.89 at 26 weeks -0.70 at 52 weeks
for 52 weeks (803 patients)	placebo + metformin + pioglitazone 45 mg	8.1	-0.42 at 26 weeks -0.29 at 52 weeks
Initial therapy			
Monotherapy <sup>6</sup>	alogliptin 12.5 mg	7.9	-0.56
for 26 weeks (329 patients)	alogliptin 25 mg		-0.59
	placebo		-0.02
Alogliptin plus a thiazolidinedione <sup>7</sup>	alogliptin 12.5 mg + pioglitazone 30 mg	8.85	-1.56
for 26 weeks	alogliptin 25 mg + pioglitazone 30 mg	8.80	-1.71
(055 pallents)	alogliptin 25 mg	8.80	-0.96
	pioglitazone 30 mg	8.76	-1.15

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First published online 12 December 2013

#### Canagliflozin

#### Approved indication: type 2 diabetes

Invokana (Janssen-Cilag) 100 mg, 300 mg tablets Australian Medicines Handbook section 10.1

Canagliflozin is the second sodium-glucose co-transporter inhibitor to be approved in Australia. Like dapagliflozin (Aust Prescr 2013;36:174-9), it reduces renal reabsorption of glucose resulting in increased excretion in the urine. The fall in the renal threshold for glucose excretion reduces blood glucose.

A single dose of canagliflozin will suppress the renal threshold for at least 24 hours. Although food does not affect bioavailability, taking canagliflozin before breakfast will reduce postprandial glucose concentrations. As canagliflozin is mainly metabolised by glucuronidation, there is a potential for its efficacy to be reduced by enzyme-inducing drugs such as phenytoin and rifampicin. An interaction with digoxin increases the concentration of digoxin. Approximately one third of the canagliflozin metabolites are excreted in the urine and there is a need to check renal function before and during treatment as canagliflozin can decrease the glomerular filtration rate (GFR). The increases in serum urea and creatinine will decline after treatment is stopped.

Efficacy declines below an estimated GFR of 60 mL/min/1.73 m<sup>2</sup> and adverse effects increase, so canagliflozin should not be used below 45 mL/min/1.73 m<sup>2</sup>. There is a risk of hyperkalaemia in patients with moderate renal impairment, particularly if they are taking ACE inhibitors or potassium-sparing diuretics. Canagliflozin is also associated with increases in serum magnesium and phosphate.

Canagliflozin has been studied as monotherapy in patients with type 2 diabetes that has not been controlled by diet and exercise. One placebocontrolled trial randomised 587 patients to take canagliflozin 100 mg or 300 mg for 26 weeks. Their mean glycated haemoglobin (HbA1c) at the start of the study was approximately 8.0% (64 mmol/mol). At the end of the study HbA1c had increased by 0.14% in the placebo group, but decreased by 0.77% with canagliflozin 100 mg and by 1.03% with 300 mg. An HbA1c below 7.0% (53 mmol/mol) was achieved by 62.4% of the canagliflozin 300 mg group and 44.5% of the 100 mg group, but only 20.6% of the placebo group. The patients on active treatment lost an average of 2.5-3.4 kg while the weight loss in the placebo group was 0.5 kg.1

Canagliflozin has also been studied in combination with other drugs for diabetes, however, at the time of writing not all of these trials have been published in full. A placebo-controlled, dose-ranging study tried five different doses in 386 patients who had mean HbA1c concentrations of 7.6–8.0% (60–64 mmol/mol) despite treatment with metformin. After 12 weeks the absolute fall in HbA1c was 0.76% with canagliflozin 100 mg and 0.92% with 300 mg daily compared with a fall of 0.22% in the placebo group.<sup>2</sup> This statistically significant difference was confirmed in a 26-week study involving 906 patients.

Canagliflozin was compared to sitagliptin in 1284 patients who had diabetes which was not controlled by metformin. The average HbA1c concentration was 7.9–8.0% (63–64 mmol/mol) at the start of the study. After 26 weeks HbA1c was reduced by 0.79% with canagliflozin 100 mg, 0.94% with canagliflozin 300 mg and by 0.82% with sitagliptin 100 mg compared with a reduction of 0.17% with placebo. The patients in the placebo group were then switched to sitagliptin. After a total of 52 weeks the mean reductions in HbA1c from baseline were 0.73% with sitagliptin and 0.73% with canagliflozin 100 mg. Canagliflozin 300 mg resulted in a reduction of 0.88% which was statistically superior to sitagliptin.<sup>3</sup>

Another trial studied patients with diabetes that was not well controlled by metformin and a sulfonylurea. A group of 378 patients added canagliflozin 300 mg daily while another 378 added sitagliptin 100 mg daily. These patients had a mean HbA1c concentration of 8.1% (65 mmol/mol). After a year this had declined by 1.03% (11.3 mmol/mol) with canagliflozin and by 0.66% (7.2 mmol/mol) with sitagliptin. At the end of the study, 47.6% of the canagliflozin group and 35.3% of the sitagliptin group had HbA1c concentrations less than 7% (53 mmol/mol). Sitagliptin had little effect on blood pressure and weight, whereas patients taking canagliflozin had a fall of 5.1 mmHg in systolic blood pressure and lost 2.3 kg.<sup>4</sup>

In another year-long trial involving 1452 patients, canagliflozin had a similar effect to glimepiride when added to metformin. The mean HbA1c concentration declined, from 7.8% (62 mmol/mol), by 0.82% with canagliflozin 100 mg, 0.93% with canagliflozin 300 mg and by 0.81% with glimepiride.<sup>5</sup> Canagliflozin can also cause additional reductions in HbA1c when glycaemic control cannot be achieved by a combination of metformin and pioglitazone.

Canagliflozin has been studied as an add-on therapy to regimens which included insulin for the treatment of type 2 diabetes. The 1718 patients were taking an average of 83 units of insulin each day. Adding canagliflozin 100 mg reduced HbA1c by 0.63% from a mean of 8.33%, while 300 mg reduced it by 0.72% from a mean of 8.27%. In a control group, adding a placebo to insulin had no significant effect on HbA1c after 18 weeks.

Several of the adverse effects of canagliflozin can be predicted from its mechanism of action. The glycosuria is associated with an increase in genital fungal infections and the osmotic diuresis can cause volume depletion. People over 75 years old and those using loop diuretics have an increased risk of dizziness and orthostatic hypotension. Hypoglycaemia is mainly a problem when canagliflozin is combined with a sulfonylurea or insulin. When canagliflozin was added to a combination of metformin and a sulfonylurea, 43.2% of patients developed hypoglycaemia and in 4% this was severe.<sup>4</sup>

There are few published data on how canagliflozin influences cardiovascular outcomes, but it does

increase concentrations of low density lipoprotein cholesterol. A study investigating the cardiovascular effects of canagliflozin found more cardiovascular events in the first 30 days of treatment with canagliflozin (13/2886 patients) than with placebo (1/1441 patients). These early events could be related to volume depletion. In an analysis of the results of nine trials there was a higher hazard ratio for strokes in patients taking canagliflozin, but this difference was not statistically significant.

The safety of canagliflozin in pregnancy and lactation is unknown. In animal studies, renal development has been affected.

While canagliflozin has been studied as monotherapy, in Australia this indication is limited to patients who cannot tolerate or have a contraindication to metformin. Canagliflozin is therefore most likely to be used as an add-on therapy. Prescribers now have an array of oral drugs to consider when type 2 diabetes cannot be controlled by metformin and a sulfonylurea, in addition to diet and exercise. Although the drugs all have an effect on the concentration of HbA1c, it is not clear which drug has the best long-term outcomes or has advantages over starting insulin. Canagliflozin may have an efficacy advantage over sitagliptin as add-on therapy.<sup>4</sup>

**T** manufacturer provided additional useful information

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First published online 26 November 2013

#### Collagenase Clostridium histolyticum

#### Approved indication: Dupuytren's contracture

Xiaflex (Actelion) vials containing 0.9 mg lyophilised powder for reconstitution

#### Australian Medicines Handbook Appendix A

Dupuytren's contracture is characterised by overproduction and deposition of fibroblasts in the hand. Longitudinal collagen cords form which cause flexion contractures. The ring finger and small finger are most commonly affected and cause considerable disability. Standard treatment is surgery to remove or release the cord, but recurrence occurs in about half of cases.

This product contains two collagenases (AUX-I and AUX-II), produced by the bacterium *Clostridium histolyticum*. These enzymes hydrolyse collagen and are used to dissolve the collagen cords.

Two placebo-controlled randomised trials – CORD I<sup>1</sup> and CORD II<sup>2</sup> – assessed the efficacy of collagenase Clostridium histolyticum in adults with Dupuytren's contracture. Patients had at least one finger contracture (with a palpable cord) of 20-100° in a metacarpophalangeal joint or 20-80° in a proximal interphalangeal joint. Approximately 40-50% of enrolled patients had previously had surgery for contractures. Collagenase Clostridium histolyticum 0.58 mg or placebo was injected into the affected cord. The volume of the injection depended on the joint being injected. If needed, the hand was manipulated the next day to facilitate cord disruption. In CORD I, patients were allowed up to three injections given monthly, whereas in CORD II, patients could have a maximum of eight injections over 12 months. Finger contracture was measured four weeks after an injection.

Significantly more patients receiving collagenase compared to placebo had their contracture reduced to 5° or less (see Table).<sup>1,2</sup> The mean number of collagenase injections required was 1.5.

In the phase III trials, recurrence rates of contracture (to at least 20 degrees) in joints that had been successfully treated with collagenase were 3.3% (28 of 838 joints) after 12 months and 42% after four years.

Injection-site reactions to collagenase were the most common events and included haemorrhage (38.2% of patients), pain (34.9%), swelling (24.5%) and tenderness (24.1%). Other common adverse events were peripheral oedema (73.5%), contusion (55%), ecchymosis (20.5%) and lymphadenopathy (13.3%).

# Table The efficacy of collagenase Clostridium histolyticum in adults with Dupuytren's contracture<sup>1,2</sup>

	CORD I trial		CORD II trial	
	collagenase	placebo	collagenase	placebo
Number of patients	204	104	45	21
Proportion of patients with reduced contracture (to 5° or less) 4 weeks after last collagenase injection	64%	6.8%	44.4%	4.8%

Most patients developed antibodies to collagenase and 15% had pruritus at the injection site. Anaphylaxis is a risk with this product.

Some patients developed serious injuries to the hand as result of the injection. These included tendon rupture, ligament injury and a complex regional pain syndrome. Patients should be warned to contact their doctor if they are unable to bend their finger after the swelling goes down.

As ecchymosis and haemorrhage were common, this drug should be used with caution in patients with a bleeding disorder or those taking anticoagulants. Except low-dose aspirin, anticoagulants should not be given up to seven days before treatment. Tetracyclines have been shown to inhibit collagen degradation and should be avoided up to 14 days before a collagenase injection.

Although collagenase is undetectable in plasma following an injection into the hand, it is a category B1 pregnancy drug and its use should be postponed until after pregnancy. Caution is urged during breastfeeding.

Collagenase injections provide a convenient option for people with Dupuytren's contracture who cannot have surgery. Approximately half of patients will benefit but complications can occur and treatment has a high relapse rate. Special training is required before a doctor can administer this product.

**T** manufacturer provided additional useful information

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First published online 12 December 2013

#### Dabrafenib

#### Approved indication: metastatic melanoma Taflinar (GlaxoSmithKline) 50 mg and 75 mg capsules Australian Medicines Handbook section 14.2.4

Like vemurafenib (Aust Prescr 2012;35:128-35), dabrafenib is indicated for patients with inoperable or stage IV metastatic melanoma with a BRAF V600 mutation. These mutations are present in about half of people with melanomas. BRAF V600E accounts for most of them (80–90%) with BRAF V600K being less common. The mutations result in expression of an abnormal protein kinase which continuously stimulates tumour cell growth. Dabrafenib is thought to slow the growth and spread of cancer cells by competitively inhibiting the abnormal BRAF kinase.

The approval of dabrafenib (150 mg orally twice daily) is based on a pivotal open-label comparative trial with dacarbazine (1000 mg/m<sup>2</sup> intravenously every three weeks). Only people with previously untreated BRAF V600E-positive melanoma and no active brain metastases were enrolled. Treatment was given until disease progressed, the patient died or adverse events were intolerable. Patients in the dacarbazine arm were allowed to cross over after confirmation of disease progression. More patients responded to dabrafenib than to dacarbazine and progression-free survival was significantly longer (see Table 1A).<sup>1</sup>

Dabrafenib has also been investigated in patients with brain metastases (1–4 lesions) but no neurological symptoms.<sup>2</sup> There was no treatment comparator in the trial. Responses appeared to be better in patients with the BRAF V600E mutation compared to those with the V600K mutation. Response rates were similar regardless of whether the patient had received local treatment (brain surgery or radiotherapy) or not (see Table 1B).<sup>2</sup>

Adverse events with dabrafenib were more common in patients with brain metastases<sup>2</sup> compared to those without brain lesions<sup>1</sup> (82% vs 53% of patients), but discontinuations because of an event were similar (3% vs 2%). In a safety cohort of 187 patients, the most common adverse reactions were hyperkeratosis (37% of patients), headache (32%), fever (28%), arthralgia (27%), skin papilloma (24%), hair loss (22%), palmar-plantar erythrodysaesthesia (20%), fatigue (19%), nausea (19%), asthenia (18%), rash (17%), vomiting (12%), cough (12%), back pain (12%), constipation (11%) and diarrhoea (11%). Hypophosphataemia (37%) and increased alkaline phosphatase (19%) also occurred frequently.

Some patients (9%) developed cutaneous squamous cell carcinoma, often in the first 12 weeks of treatment. New primary melanomas were also reported so regular skin examination is recommended. Lesions should be excised and treatment can continue.

Uveitis and iritis have been reported with dabrafenib so vision should be monitored. Pancreatitis can occur and investigation of unexplained abdominal pain should include tests for serum lipase. Monitoring serum glucose is recommended for patients with diabetes or high blood sugar as hyperglycaemia was a problem in the trials. Treatment interruption is recommended if renal failure or fever develops.

Dabrafenib should be taken one hour before or two hours after a meal. If a dose is missed, it should not be taken within six hours of the next dose. Following oral administration, peak plasma concentrations of dabrafenib are reached after two hours. Its terminal half-life is eight hours and the dose is excreted in the faeces (71%) and urine (23%). Although there are no clinical data, dabrafenib exposure could potentially be increased in patients with moderate to severe hepatic impairment, and caution is urged.

Dabrafenib is metabolised by cytochrome P450 (CYP) 2C8 and 3A4 so inhibitors of these enzymes, such as ketoconazole and gemfibrozil, increase dabrafenib exposure. Potent CYP 2C8 inducers such as rifampicin, phenytoin and St John's wort should be avoided.

Dabrafenib induces UDP glucuronosyl transferase and numerous cytochrome enzymes (CYP3A4, 2C9, 2B6, 2C8 and 2C19) so it may lower serum concentrations of many drugs including midazolam, warfarin, hormonal contraceptives, dexamethasone and immunosuppressants. Drugs that increase gastric pH, such as proton pump inhibitors and H2 antagonists, could potentially reduce the bioavailability of dabrafenib.

Dabrafenib may prolong progression-free survival in patients with inoperable or metastatic melanoma. However, patients must have a confirmed BRAF V600 mutation before they can start treatment. It is

#### Table 1 Efficacy of dabrafenib in BRAF V600-positive metastatic melanoma

#### A Patients without brain metastases – phase III trial <sup>1</sup>

	dabrafenib	dacarbazine
Mutation	BRAF V600E (187 patients)	BRAF V600E (63 patients)
Response rate	50% (6 complete responses, 87 partial responses)	7% (1 complete response, 3 partial responses)
Median progression-free survival	5.1 months	2.7 months
12-month overall survival	70%	63%

#### **B** Patients with brain metastases – phase II trial <sup>2</sup>

	Gabratenib			
Mutation	BRAF V600E		BRAF V600K	
Patients	untreated brain metastases (74 patients)	progressive brain metastases after local treatment (65 patients)	untreated brain metastases (15 patients)	progressive brain metastases after local treatment (18 patients)
Overall intracranial response rate	39.2% (2 complete responses, 27 partial responses)	30.8% (20 partial responses)	6.7% (1 partial response)	22.2% (4 partial responses)
Median progression-free survival	3.7 months	3.8 months	1.9 months	3.6 months
Median overall survival	7.6 months	7.2 months	3.7 months	5.0 months

not yet known how dabrafenib will compare to other treatments for this disease such as vemurafenib and ipilimumab.

**T** manufacturer provided additional useful information

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#### Tolvaptan

#### Approved indication: hyponatraemia

Samsca (Aspen) 15 mg and 30 mg tablets Australian Medicines Handbook section 10.6.2

Hyponatraemia is a common electrolyte abnormality. It can be associated with heart failure, cirrhosis and the syndrome of inappropriate antidiuretic hormone secretion (see Aust Prescr 2011;34:42-5).

Unless there is hypovolaemia, hyponatraemia is usually treated with fluid restriction. Additional treatment is needed if severe hyponatraemia persists and the patient remains symptomatic.

A new approach is to target the action of antidiuretic hormone (vasopressin). Tolvaptan is an antagonist at the vasopressin  $V_2$  receptor. By blocking the binding of antidiuretic hormone to the receptor, tolvaptan increases the excretion of water. As there is no significant change in sodium excretion, the serum concentration of sodium increases.

The serum sodium begins to rise 2–4 hours after an oral dose, with a peak effect at 4–8 hours. Treatment is given once a day, starting at 15 mg. The dose can be increased, but the effect on serum sodium does not increase beyond 60 mg daily.

Tolvaptan is mainly metabolised by cytochrome P450 3A. Co-administration with inducers or inhibitors of this enzyme should be avoided. The tablets should not be taken with grapefruit juice. No dose adjustment has been recommended for patients with liver disease. Anuria, hypovolaemia and an inability to sense thirst are contraindications.

In a small open-label trial, tolvaptan was compared to fluid restriction in 28 inpatients with euvolaemic or hypervolaemic hyponatraemia. These patients had serum sodium concentrations below 135 mmol/L. There was a significant increase in serum sodium four hours after the first dose of tolvaptan. By day four of treatment serum sodium was normal in 50% of the tolvaptan group. It took until day eight for sodium to return to normal in 50% of the fluid restriction group.<sup>1</sup>

Two double-blind trials then randomised 225 patients to take tolvaptan and 223 to take placebo for up to 30 days. The patients were euvolaemic or hypervolaemic with sodium concentrations below 135 mmol/L. Approximately half the patients only had mild hyponatraemia (130–134 mmol/L). The sodium concentration increased significantly more with tolvaptan than with placebo. In the tolvaptan groups, 40–55% of patients had a normal serum sodium by the fourth day of treatment, compared with 11–13% of the placebo groups. By day 30, the respective figures were 53–58% and 25%.<sup>2</sup>

The most common adverse effects of tolvaptan were thirst and dry mouth. Serious adverse events include dehydration, acute renal failure and ascites.<sup>2</sup> As increasing the excretion of water will raise the concentration of potassium, as well as sodium, some patients will be at risk of hyperkalaemia.

Acute severe hyponatraemia is a medical emergency, but tolvaptan has not been studied in this setting. It is not recommended for use with hypertonic saline.

If the serum sodium rapidly rises there is a risk of cerebral demyelination. Fluid restrictions should generally be lifted when tolvaptan is started to reduce the chance of a rapid rise. The restrictions can be resumed after treatment, especially as serum sodium will tend to fall when tolvaptan is stopped.<sup>2</sup> In view of the need to titrate the dose and monitor electrolytes, tolvaptan should be started in hospital.

While tolvaptan can correct the serum sodium in a proportion of patients with hyponatraemia, its clinical role is unclear. It is important to manage the underlying causes of hyponatraemia. Although hyponatraemia is associated with increased mortality in patients with cirrhosis, the safety and efficacy of tolvaptan has not been established in this group. There is some evidence that the drug increases the risk of gastrointestinal bleeding in patients with cirrhosis. The efficacy of tolvaptan in heart failure is also uncertain. It did not significantly reduce the length of hospital stay for patients with heart failure and hyponatraemia.<sup>3</sup>

**T** manufacturer provided the product information

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The Transparency score (**T**) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

- \* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).
- <sup>+</sup> At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).
- A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration

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