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EDITORIAL

Electronic medication management: is it a silver bullet?

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Electronic medication management has been developed to improve patient safety by increasing the legibility of prescriptions, implementing passive and active decision support and allowing access to medical records across a wide area.[1] It is a patient safety initiative, albeit some stakeholders see it as a cost-saving exercise. Electronic medication management is a broad term covering all computer systems involved. It is a closed loop system that encompasses prescribing, administration, pharmacy review, smart infusion pumps, automated dispensing cabinets, barcode medication administration and anything that has electronic medicines datasets or encompasses medication management processes.[2]

There are a number of electronic medication systems available. These vary from software for individual practitioners to stand-alone systems for specialties (e.g. oncology, intensive care), and hospital or district-wide systems with or without an integrated, fully electronic medical record.

Electronic prescribing keeps track of medicine use through computer applications. With district-wide systems, this record is available across all sites within the local health district for transfers or future admissions. For example, when a patient is discharged from a hospital in NSW, the discharge script is printed from the software and the discharge medication list is exported in the electronic discharge summary for transmission to GPs, NSW HealtheNet and My Health Record.

An electronic prescribing system provides an easily accessible record of administration. It improves access to medication histories across the continuum of care from the GP to the hospital and back to the GP.

Data and reports available in electronic prescribing systems allow audits on drug use, including tracking orders for antimicrobial stewardship, medicine recalls and analysis of usage patterns. The software can incorporate standardised prescribing protocols for specific conditions, for example pain management, vaccinations and acute coronary syndromes.

Responses to drug shortages across a health district can be coordinated with alerts and suggestions for alternatives. These can be deployed across all sites rapidly.

One of the main benefits of using an electronic prescribing system is that the software improves overall legibility. A clear, typed prescription decreases interpretive errors. The person reviewing or administering does not need to decipher illegible handwriting and error-prone abbreviations.

Electronic prescribing also reduces the risk of dosing errors as it can specify commonly used doses. Potentially dangerous doses are minimised as the software guides prescribers towards using the more common doses. This does not, however, prevent all of these errors as the software needs to provide flexibility during prescribing. For example, restricting oral methotrexate to a maximum of 30 mg on one day per week would prevent prescribing of the higher doses (up to 100 mg) required for medical management of ectopic pregnancy.

Recording of electronic prescribing and administration also allows the standardisation of orders and can provide clinical alerts. For example, if clozapine is prescribed, a message to contact the clozapine coordinator can appear along with the investigations required for safe prescribing.

Electronic prescribing can also help to prevent the prescribing of drugs to patients with medication allergies by recording allergy and adverse drug reaction information. When allergies are correctly entered into the system, the software alerts the prescriber with details of the allergy. Unfortunately, even with prompts within the system, not all patients have their allergies recorded, some allergies are recorded incorrectly, and in larger organisations there may be multiple silos of allergy data with details recorded in other sections of the patient record that are not accessible to the electronic prescribing system.

Another issue with managing allergies is that it does not prevent clinicians from entering incorrect information (simple user error). For example, a prescriber could enter penicillamine allergy for a substance allergy when they mean penicillin. In the electronic prescribing software, the specific substance is benzylpenicillin or phenoxymethylpenicillin and the allergy group is penicillin.

With any electronic prescribing system comes an opportunity to provide knowledge-based clinical decision support at the time of prescribing or administration. However, this needs to be balanced with the risk of alert fatigue.[3] The commonest source of alerts is for drug interactions. Unfortunately, in

some systems the drug interactions detected can be over-inclusive, and trivial or minor potential interactions can fire the same or very similar styles of alert as potentially life-threatening ones. As a result, the flurry of much more common, unimportant alerts trains the user to ignore all alerts including the important ones.

Another frequent source of alerts is therapeutic duplication which warns if two drugs of the same class are prescribed simultaneously. Here, the usefulness of such alerts depends heavily on the definitions of the therapeutic classes.

If, for example, all corticosteroids are put into one class then an alert will fire (inappropriately) when a patient with asthma on preventative puffers is prescribed prednisolone for an acute exacerbation. Having heparins and oral anticoagulants in one therapeutic class will provide an appropriate alert when enoxaparin is inadvertently prescribed as bridging therapy for a patient starting on rivaroxaban, but an inappropriate alert if that patient was starting on warfarin. A warning regarding multiple antipsychotics may be important to a junior medical officer on a general medical ward, but to a psychiatrist in a mental health unit it may be annoying.

In our own implementation of an electronic prescribing system for the Hunter New England Local Health District, the Quality Use of Medicines Committee turned off drug interaction warnings on the advice of sites already using the software. However, we have continued the alerts for therapeutic duplication. Our preliminary analysis shows that 95% of duplicate therapy warnings are not immediately actioned. However, what about the 5% that are actioned? Has this made a significant impact?[4] In a system as complex as a large heath district, it is difficult to isolate cause and effect. The Quality Use of Medicines Committee has decided to remove duplicate therapy warnings provided by the software vendor and replace them with specific tailored alerts determined by local expertise. The goal is to make every alert relevant to that prescribing or administration circumstance. As the software matures, we hope to nuance our warnings and alerts.

The implementation of electronic prescribing across our district has improved patient safety, communication and accountability, and provides an electronic record of medication prescribing and administration. However, ongoing work needs to be done to address problems with alerts, developing protocols, adding new medications and overall system improvements. We need to improve usability to increase engagement while maintaining the focus on patient safety. ≺

Conflict of interest: none declared

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ARTICLE

The cost of asthma medicines

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SUMMARY

Most adults and adolescents with asthma require a preventer inhaler. In Australia these patients are often prescribed a combination inhaler containing a corticosteroid and a long-acting beta$_2$ agonist.

These combination inhalers increase the cost of treatment for patients and for government and may not provide extra benefit. Many patients can control their asthma using an inhaled corticosteroid alone for prevention of symptoms and flare-ups.

Most of the benefits of inhaled corticosteroids are obtained at low doses. To achieve these benefits it is important to check that the patient is using their inhaler correctly and regularly.

Shared decision making includes discussing the options for treatment. Offering a more affordable preventer regimen could aid adherence and lead to improved outcomes.

Introduction

Australian guidelines recommend that most adults and adolescents with asthma should be taking a preventer inhaler. This is to minimise symptoms, prevent a decline in lung function, and to reduce the risk of exacerbations and asthma-related death.[1] For the majority of patients, most of these benefits can be achieved with low-dose inhaled corticosteroids (e.g. beclometasone 200 micrograms/day, budesonide 400 micrograms/day, ciclesonide 160 micrograms/day or fluticasone propionate 200 micrograms/day). However, in Australia, most patients are prescribed inhaled corticosteroids in combination with long-acting beta$_2$ agonists,[2,3] often at moderate or high doses.[2] This is common practice, despite these combination products not being subsidised by the Pharmaceutical Benefits Scheme (PBS) for the initial treatment of asthma.

Adherence is higher with combination inhalers than it is with inhaled corticosteroids alone. However, Australian data show that less than 20% of patients are being dispensed enough of either of these types of preventer inhaler to be taking their treatment regularly.[2]

Cost considerations

Out-of-pocket cost is a major factor contributing to poor adherence to treatment,[4] including in Australia[5] where most medicines are subsidised by the PBS. Patients may not necessarily be comfortable telling a doctor their concerns about prescription costs, but pharmacists frequently see cost-related decisions being made at the point of purchase. This is particularly the case for asthma, since short-acting reliever inhalers, such as salbutamol, are cheaper than inhaled corticosteroids and have a rapid effect. However, reliance on reliever inhalers, especially without a preventer, increases the risks of severe asthma exacerbations.[6]

Many clinicians are not aware that the average cost for patients with most low-dose corticosteroid-only preventers is substantially lower than treatment with a combination inhaled corticosteroid and long-acting beta$_2$ agonist. There are several options for prescribing low-dose preventers for adults that give the lowest average monthly out-of-pocket cost for the patient. Consider the dose, the frequency of administration and the number of actuations (single metered doses) in each inhaler (see Table). When averaged over a year, the cost of a low-dose inhaled corticosteroid can be strikingly low, as little as 15–30% of the out-of-pocket cost of any combination inhaler.

Inhaled corticosteroids are very effective – low dose and affordable cost do not mean low benefit

For most patients, 80–90% of the benefit of inhaled corticosteroids is obtained with low doses, if taken regularly and correctly. For example, in a large community study, the risk of dying of asthma was lower for patients who were dispensed four or more low-dose corticosteroid inhalers per year compared with those who received none.[7] In a large randomised controlled trial, the risk of serious exacerbations (emergency department visits, hospitalisations, death) was also halved and symptoms were significantly reduced with regular use of budesonide 400 micrograms/day, even in patients with symptoms as infrequent as once a week or less.[8]

Table **Minimising the costs of asthma therapy**

Drug	Formulation (micrograms per actuation)	Maximum price to patient per script		Total actuations per script	Regimen to achieve low total inhaled corticosteroid dose* (actuations)	Number of months supply from one script	Maximum cost to patient per month (30 days)	
		General	Concession				General	Concession
Low-dose inhaled corticosteroid-only treatment								
Budesonide (dry powder inhaler)	400	$39.50	$6.40	200	1 once daily	6.7	$5.93	$0.96
Ciclesonide (pressurised metered-dose inhaler)	160	$39.50	$6.40	120	1 once daily	4.0	$9.88	$1.60
Beclometasone (pressurised metered-dose inhaler)	100	$39.09	$6.40	200	2 once daily (or 1 twice daily)	3.3	$11.73	$1.94
Fluticasone (dry powder inhaler)	100	$24.16	$6.40	60	1 twice daily	1.0	$24.16	$6.40
Low-dose inhaled corticosteroid/long-acting beta$_2$ agonist combination treatment								
Budesonide/formoterol (eformoterol) (dry powder inhaler)	100/6	$39.50	$6.40	120	2 twice daily	1	$39.50	$6.40
Budesonide/formoterol (eformoterol) (dry powder inhaler)	200/6	$39.50	$6.40	120	2 once daily (or 1 twice daily)	2	$19.75	$3.20
Fluticasone propionate/formoterol (eformoterol) (pressurised metered-dose inhaler)	50/5	$39.50	$6.40	120	2 twice daily	1	$39.50	$6.40
Fluticasone propionate/salmeterol (dry powder inhaler)	100/50	$39.50	$6.40	60	1 twice daily	1	$39.50	$6.40
Low-dose inhaled corticosteroid and long-acting beta$_2$ agonist treatment in separate inhalers †								
Ciclesonide (pressurised metered-dose inhaler)	160	$39.50	$6.40	120	1 once daily	4.0		
• with formoterol (eformoterol) (dry powder inhaler) OR	6	$33.24	$6.40	60	1 twice daily	1.0	Total $43.12	Total $8.00
• with salmeterol (dry powder inhaler)	50	$39.50	$6.40	60	1 twice daily	1.0	Total $49.38	Total $8.00
Beclometasone (pressurised metered-dose inhaler)	100	$39.09	$6.40	200	2 once daily (or 1 twice daily)	3.3		
• with formoterol (eformoterol) (dry powder inhaler) OR	6	$33.24	$6.40	60	1 twice daily	1.0	Total $44.97	Total $8.34
• with salmeterol (dry powder inhaler)	50	$39.50	$6.40	60	1 twice daily	1.0	Total $51.23	Total $8.34

* The low total daily inhaled corticosteroid dose is based on the Australian Asthma Handbook table of inhaled corticosteroid doses for adults – www.asthmahandbook.org.au/table/show/22. For each drug, this column shows how to prescribe a low-dose inhaled corticosteroid regimen with the lowest patient copayment. These regimens are based on the recommended number of actuations and dosing frequency in the approved product information. The calculations were based on 2018 costs and copayments, available from www.pbs.gov.au.

† Separate inhalers should only be prescribed if a suitable combination inhaler is not available, and the clinician is certain that the patient will continue to take the inhaled corticosteroid regularly, and the patient can use the two different inhaler devices correctly.

Using a preventer inhaler correctly reduces treatment costs

Patients can save costs by using their inhaler correctly. If their inhaler technique is incorrect, the drug is being wasted, as it does not reach the airways. This is the case for such a high proportion of patients (up to 80%) that inhaler technique can be assumed to be incorrect until proven otherwise. Health professionals need to know the correct technique for the type of inhaler being prescribed, and watch the patient using it. Clear step-by-step videos are available online (www.nationalasthma.org.au/health-professionals/how-to-videos, www.nps.org.au/medical-info/consumer-info/inhaler-devices-for-respiratory-medicines).

Book a review visit if treatment has been started or changed

Patients usually start to feel the benefit from inhaled corticosteroids quite quickly, within 1–2 weeks, and they continue to improve for up to 18 months. If their asthma symptoms are still not controlled after 2–3 months, check adherence and inhaler technique before considering stepping up treatment to a combination of a low-dose inhaled corticosteroid and a long-acting beta$_2$ agonist.

Combining a corticosteroid with a long-acting beta$_2$ agonist reduces exacerbations on average by 20%. These can be reduced further if low-dose budesonide/formoterol (eformoterol) is prescribed as 'maintenance and reliever therapy', that is as both the patient's regular maintenance inhaler (usually twice daily) and as their reliever inhaler (instead of salbutamol). However, contrary to expectations, adding a long-acting beta$_2$ agonist has surprisingly little effect on the use of reliever inhalers.[9] After asthma has been well-controlled for 2–3 months, treatment can be gradually stepped down to find the patient's minimum effective dose.

Shared decision making improves asthma outcomes

Shared decision making, either when treatment is first discussed or at a review visit, improves adherence and asthma outcomes.[10] As clinicians, we need to be aware of the contribution out-of-pocket costs have to patients' day-to-day adherence, and to know the cost implications of what we prescribe. For some patients, offering a more affordable option may make the difference between their choosing to take a regular preventer inhaler, and 'making do' with a reliever alone, with the attendant risk of worse outcomes. Given the difference in cost, many patients may be interested in trying an inhaled corticosteroid-only inhaler first, rather than a combination inhaler, if the likely benefit and its time course are explained. <

Helen Reddel has received honoraria for providing independent advice on advisory boards, steering committees and data safety monitoring boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck and Novartis. She has received honoraria for independent consulting for AstraZeneca and GlaxoSmithKline, and for providing independent medical education at symposia funded by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, Novartis and Teva. Professor Reddel has received independent research grants from AstraZeneca and GlaxoSmithKline.

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FURTHER READING

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ARTICLE

'Cephalosporin allergy' label is misleading

SUMMARY

Penicillins and cephalosporins can cause a similar spectrum of allergic reactions at a similar rate.

Cross-reactive allergy between penicillins and cephalosporins is rare, as is cross-reaction within the cephalosporin group. Patients should therefore not be labelled 'cephalosporin-allergic'.

Cross-reactive allergy may occur between cephalosporins (and penicillins) which share similar side chains.

Generally, a history of a penicillin allergy should not rule out the use of cephalosporins, and a history of a specific cephalosporin allergy should not rule out the use of other cephalosporins.

Specialist advice or further investigations may be required when the index reaction was anaphylaxis or a severe cutaneous adverse reaction, or when the antibiotics in question share common side chains.

When recording a drug allergy in the patient's records, it is important to identify the specific drug suspected (or confirmed), along with the date and nature of the adverse reaction. Records need to be updated after a negative drug challenge.

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CPD FOR PHARMACISTS

This article has a continuing professional development activity for pharmacists available at https://learn.nps.org.au

Introduction

To label an individual with a 'cephalosporin allergy' is misleading. Given the structural diversity of the cephalosporin family, hypersensitivity is seldom a class effect but is much more likely to relate to the individual drug. Cross-reactivity within the family is very limited and is more likely to relate to the side chain than the core structure.[1] A greater awareness of this in clinical practice would lead to the availability of alternative cephalosporins and prevent unnecessary use of other classes of broad-spectrum antibiotics.

Cephalosporins were first introduced in the 1960s,[2] and are one of the most commonly used first-line antibiotics.[3] They have a beta-lactam ring linked to a six-member dihydrothiazine ring[4] with additional side chains at the R1 and R2 location (Fig. 1). Cephalosporins are commonly classified by their 'generations' (first to fifth) which relates to the order of their development (not their efficacy) and has relevance to antibacterial spectrum and beta-lactamase resistance. Their chemical structure tends to become more complex with successive generations. This classification has limited relevance to allergy and allergic cross-reactivity.

Cephalosporins cause allergic reactions with a similar spectrum and incidence to that of other antibiotics, such as penicillins.[5] Reactions include type I hypersensitivity (urticaria, angioedema, anaphylaxis), and type IV hypersensitivity (maculopapular exanthem, severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis or acute generalised exanthematous pustulosis or organ hypersensitivity).

Structural chemistry and allergy

Immunological reactivity to small molecules such as antibiotics depends on the formation of haptens. These are stable covalent complexes of the drug with larger carrier molecules such as serum or membrane proteins. For penicillin, this occurs when the beta-lactam ring spontaneously opens to form penicilloyl which binds to lysine residues on host proteins.[6]

Beta-lactam ring

Cephalosporins and penicillins share the four-atom beta-lactam ring structure. In penicillins the beta-lactam ring is linked to a five-member thiazolidine ring whereas in cephalosporins it is linked to the dihydrothiazine ring (see Figs 1 and 2).

It was previously thought that people allergic to penicillins had a high likelihood of allergy to any cephalosporins (reportedly up to 23.9%).[7] More recent studies have demonstrated cross-reactivity rates as low as 1%.[8]

The common beta-lactam ring is the putative reason for potential cross-reactivity between penicillins and cephalosporins. However, there is in fact little theoretical basis for this. Penicillins are chemically reactive due to a high degree of tension between the beta-lactam ring and the thiazolidine ring, whereas the cephalosporin beta-lactam ring forms a more

Fig. 1 **General structure of cephalosporins**

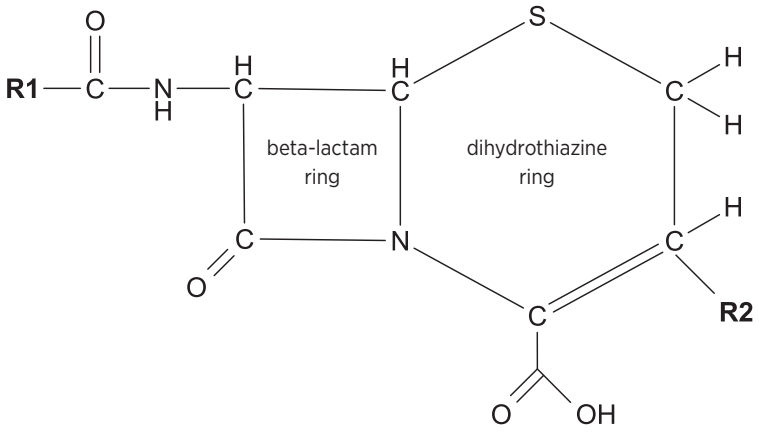
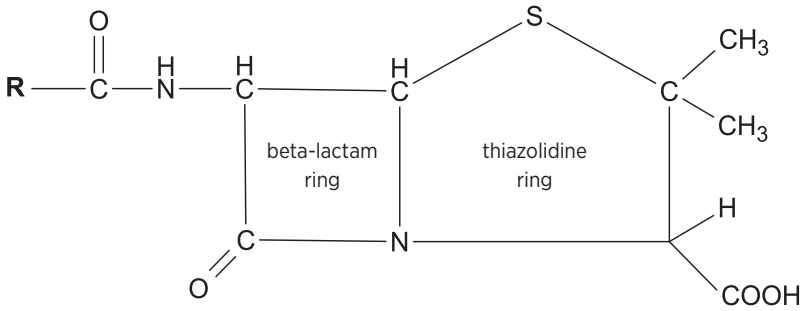


Fig. 2 **General structure of penicillins**



stable structure with its dihydrothiazine ring. This makes haptenisation of proteins with cephalosporins a slower and less efficient process. Also, when the cephalosporin beta-lactam ring is disrupted to form a cephalosporyl determinant, this structure is unstable and fragments rapidly so it is not antigenic.[9]

Cross-reactive side chains

Studies have revealed that the side chains of beta-lactam antibiotics are important antigenic determinants in allergy (Table). For example, if someone reacts to the amino side chain of amoxicillin rather than the beta-lactam core structure, they are likely to have a cross-reactive allergy to ampicillin which shares a very similar side chain, but not to benzylpenicillin or other penicillins.[10]

Antigenic determinants for cephalosporin hypersensitivity have only recently become better defined. The cephalosporin R2 side chain is usually lost after the opening of the beta-lactam ring, so is less likely to cause allergy (Fig. 1). It is thought that the R1 side chain determines the specificity of immunological reactions to cephalosporins.[11] For this reason, cross-reactive allergy across the whole cephalosporin family is seldom if ever seen.

The R1 side chain as an antigenic determinant appears to explain the cross-reactivity that can be seen between certain beta-lactam antibiotics, as well as within the cephalosporin family. For example, aminopenicillins such as ampicillin and amoxicillin have similar R1 side chains to the aminocephalosporins cefalexin and cefaclor, and patients with sensitisation to the amino side chain have a risk of cross-reactive allergy between amoxicillin and cefalexin but can tolerate other (non-amino) penicillins and cephalosporins without this side chain.

Predicting cross-reactivity

Of the cephalosporins currently available in Australia, similar or identical side chains can be found within the same generation, such as in the third-generation cephalosporins cefotaxime and ceftriaxone, or across generations, such as in cefalexin (first generation) and cefaclor (second generation), and in cefalotin (first generation) and cefoxitin (second generation) (Table). However, predicting cross-reactivity among the cephalosporins remains challenging and reactivity may be due to the entire cephalosporin molecule and not just the R1 side chain (Table).[1] A special case is the well-known phenomenon of cefaclor serum sickness-like reaction, occurring most commonly in childhood, which is not cross-reactive with other cephalosporins or penicillins (see Box).[12-16]

Investigations

Blood tests (immunoassays) for specific IgE antibodies (sIgE) (formerly known as RAST) to penicillin, amoxicillin and cefaclor are available but have very limited sensitivity. The positive predictive value is high but the negative predictive value is low, therefore a negative blood test does not rule out allergy. Tests are not available for the majority of cephalosporins.[17] The basophil activation test may have more diagnostic accuracy,[18] but is currently only available in research laboratories.[19]

Skin prick, intradermal (early or delayed) and patch testing are more sensitive than immunoassays, however their negative predictive values are not established due to a lack of sufficiently powered studies.[20] Several cephalosporins are not available in a solution suitable for skin testing due to poor solubility, and the diagnostic value of extemporaneously prepared solutions has not been established. Skin-test sensitivity to cephalosporins can decrease over time[21] which complicates interpretation. If the skin test is positive to the index drug, then a negative skin test to a related drug might help to exclude cross-reactive allergy. However, this would need to be confirmed by oral or parenteral challenge.

Challenge testing

Challenge testing should only be done at specialist discretion. This involves the deliberate administration of a cephalosporin, usually in graded dosage. It should be carried out under expert supervision in a centre with facilities to manage acute allergic reactions. It is the gold standard test for patients with a history of allergy to a cephalosporin.

Testing with a drug putatively linked to a previous reaction (homologous challenge) is warranted when there is an indication to use the drug, if there is significant uncertainty about the history, or if the reaction occurred in the distant past. In low-risk cases (mild reactions, history suggesting index reaction intolerance rather than allergy), oral rechallenge without prior skin testing can be considered to facilitate delabelling.

A history of a severe delayed-type 4 hypersensitivity reaction (Stevens-Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) is considered a permanent contraindication to challenge testing since the T-cell immunological memory is likely to persist.[22] A history of immediate allergy and even anaphylaxis is not an absolute contraindication to (cautious) challenge since type 1 allergy frequently resolves over several years[21,23] and a negative challenge clears the drug for future use.

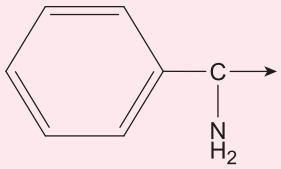
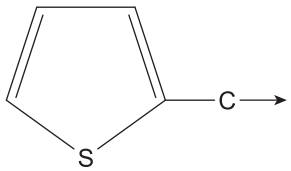
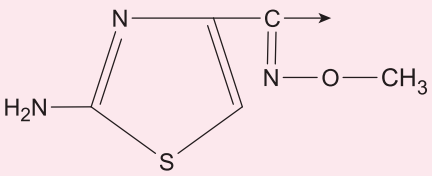
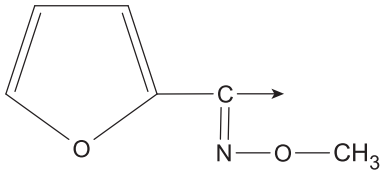
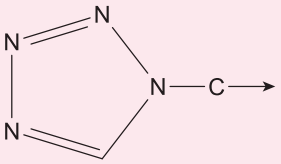
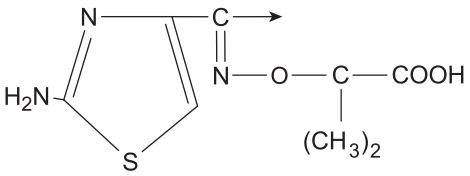
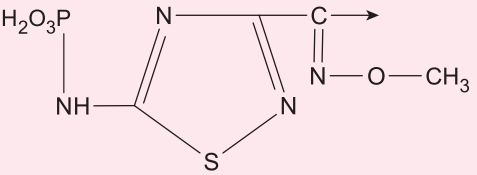
When the index drug is known, and is found positive on sIgE blood test, skin prick or intradermal testing, then the challenge is done with an alternative cephalosporin with a different R1 side chain (heterologous challenge) as this may show the absence of cross-reactive allergy. In the event of severe anaphylaxis to a specific cephalosporin, the specialist may opt to challenge with an alternative beta-lactam, despite negative in vitro and in vivo testing (Fig. 3). For a patient labelled with 'cephalosporin allergy' in which the index cephalosporin is not known, a cautious challenge may be warranted with the cephalosporin that is most likely to be useful.

Recording a patient's allergy

Clinical history is of paramount importance when recording a reaction. This should include the indication for the antibiotic used, comorbidities, and concurrent drugs. A detailed description of the reaction is essential, including the date and the actual name of the drug rather than the family or class of drug. Electronic health records may facilitate recording of such details.

The term 'cephalosporin allergy' should not be used. It is inaccurate and indicates a contraindication to the entire class of cephalosporins. Concepts of drug allergy have changed and we now know that such a blanket contraindication is usually inappropriate.

Table **Cephalosporins and penicillins grouped by R1 side chain similarity**

R1 side chain	Cephalosporin	Penicillin
	cefaclor, cefalexin	ampicillin, amoxicillin*
	cefoxitin, cefalotin	
	cefotaxime, ceftriaxone, cefepime	
	cefuroxime	
	cefazolin	
	ceftazidime	aztreonam
	ceftaroline	

* Amoxicillin has an additional hydroxyl group.

Box Serum sickness-like reactions with cefaclor

Cefaclor is associated with serum sickness-like reactions in children and sometimes adults. This is characterised by rash, fever, arthralgia, arthritis and lymphadenopathy, but serum complement concentrations are not reduced and immune complexes have not been identified. The mechanism is thought to be due to the genetically determined biotransformation of the drug to produce lymphocytotoxic metabolites.[12]

Patients who suffer this reaction may acquire a 'cephalosporin allergy' label. However, this is incorrect because, although patients may have a recurrence on rechallenge with cefaclor, in vitro studies have shown a lack of cross-reactivity with similar molecules[12,13] and patients have been shown to tolerate other cephalosporins.[14-16]

Recommendations

In general:

- a history of penicillin allergy should not rule out the use of cephalosporins
- a history of allergy to a specific cephalosporin should not rule out the use of other cephalosporins.

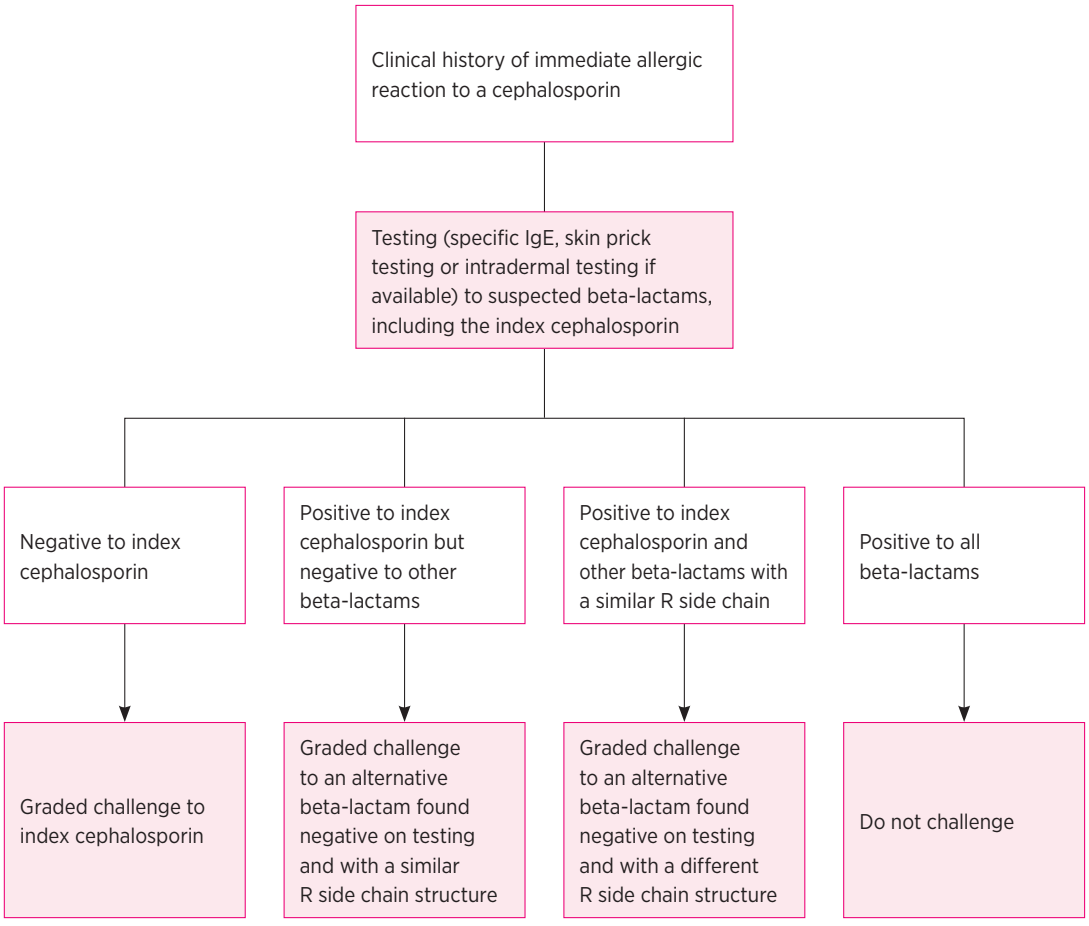
Exceptions include when:

- the index reaction was anaphylaxis or a severe cutaneous adverse reaction
- the antibiotics in question share common side chains.

In these circumstances, specialist advice or investigation is recommended. <

Conflict of interest: none declared

Fig. 3 Decision tree for patients with a history of an immediate (anaphylactic) reaction to a cephalosporin



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ARTICLE

Antihistamines and allergy

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SUMMARY

There is now little role for sedating antihistamines in allergic conditions. Less sedating antihistamines are equally efficacious.

The less sedating antihistamines can be taken long term with no loss of efficacy, and an ongoing good safety profile.

Antihistamines have no role in the acute management of anaphylaxis.

Introduction

Antihistamines are used in the management of allergic conditions. They are useful for treating the itching that results from the release of histamine.

The early so-called 'first generation' antihistamines, such as promethazine, caused sedation. This is less of a problem with newer 'second generation' antihistamines, such as loratadine, and 'third generation' antihistamines such as desloratadine.

The oral antihistamines available in Australia to treat allergic conditions are listed in the Box. Desloratadine and fexofenadine are registered for use in infants six months and older, while loratadine and cetirizine can be used from 12 months of age. Some antihistamines are used for their antinausea or sedative properties.

Pharmacology

Antihistamines bind to histamine receptors on the surface of cells. There are four types of histamine receptors in the body (H_1-H_4), with H_1 and H_2 being most widely expressed.[1]

H_1 histamine receptors are found on a variety of cells including airway and vascular smooth muscle cells, endothelial cells, epithelial cells, eosinophils and neutrophils.[2] Although the receptors bind histamine, they can also signal constitutively without histamine binding to the cell surface. There is a balance between the active and inactive forms of the receptor.[1] The presence of histamine stabilises the receptor in its active form while antihistamines stabilise the inactive form of the receptor. The H_1 antihistamine drugs therefore act as inverse agonists.[1]

Loratadine is metabolised in the liver, while cetirizine, desloratadine and fexofenadine are not metabolised extensively. Cetirizine is eliminated in the urine, while fexofenadine is excreted in the faeces. Dose reduction should be considered in patients with severe liver or kidney dysfunction.[1]

Avoid sedating antihistamines

The sedating, first generation antihistamines now have little role in therapeutics. Their unfavourable adverse effect profile has prompted the Global Allergy and Asthma European Network to recommend making these antihistamines prescription-only, rather than over-the-counter, drugs.[3] The main concerns are their sedative properties and interference with rapid eye movement sleep.[3,4] Studies have shown poorer school performance in children with allergic rhinitis treated with sedating antihistamines, compared to children treated with non-sedating antihistamines and healthy children.[5] Sedating antihistamines have been found to be a cause of aviation accidents.[3] An audit of media reports found a number of car accidents attributed to sedating antihistamines, but none attributed to less sedating antihistamines.[3]

There is also concern about the use of promethazine in children less than two years old as serious behavioural and other adverse effects can occur.[3] This led to a black box warning by the US Food and Drug Administration (FDA) in 2004. Sedating antihistamines can also have anticholinergic effects that can be particularly problematic in older patients who are more susceptible to adverse effects such as dry mouth, urinary retention and delirium.[6]

Box **Oral antihistamines available in Australia**

Sedating H_1 antihistamines	Less sedating H_1 antihistamines
Cyproheptadine	Cetirizine
Dexchlorpheniramine	Desloratadine
Pheniramine	Fexofenadine
Promethazine	Loratadine
Trimeprazine	

Other sedating H_1 antihistamines include doxylamine and diphenhydramine, used for sedation, and cyclizine, used mainly as an antiemetic.

Sedating antihistamines are still favoured by some, as parenteral formulations are available. However, for promethazine there is a risk of severe tissue injury, including gangrene, with both intramuscular and intravenous administration.[7] The risk is higher for intravenous use and led to an FDA warning.[8]

The main role for sedating antihistamines is in pregnancy, where they can be used for any of the common indications for antihistamines, as they have the strongest evidence of safety. They have been taken by a large number of pregnant women and women of childbearing age without any proven increase in malformations or harm to the fetus. An exception is promethazine for which adverse events have been reported in animal studies (at very high doses). However, pregnant women must be warned about the other aspects of safety such as sedation and consider whether they should not drive while taking these drugs. The newer antihistamines are likely to be as safe in pregnancy but have not been used by as many women, so they do not have the same evidence of safety.

Newer antihistamines

The newer H_1 antihistamines are less sedating. While all the newer drugs appear equally efficacious in limited studies, there are few long-term head-to-head studies.[9] The patient can therefore choose the particular drug that they find works best, or the formulation (tablet size) that suits them. For paediatric suspensions, the choice may be determined by a preferred flavour.

Allergic rhinitis

Allergic rhinitis refers to nasal inflammation due to the release of histamine and other mediators from IgE-mediated mast cell degranulation in the nose. Other conditions may cause similar symptoms, but they can be distinguished from allergic rhinitis by allergy testing to confirm positive allergen-specific IgE to specific triggers. Allergic rhinitis may be seasonal (usually due to grass, tree or weed pollens) or perennial (due to triggers such as pet hair, house dust mite or mould). It is important to ask the patient if they also have respiratory symptoms as a worsening in allergic rhinitis can lead to increased asthma symptoms.

Avoiding trigger factors is the first step in the management of allergic rhinitis but some triggers can be difficult to avoid. Drugs can help and oral antihistamines are one of the mainstays of treatment. They are particularly useful for nasal itchiness, sneezing and rhinorrhoea, but are less effective for nasal obstruction. Oral antihistamines also have the benefit of treating associated conjunctival symptoms.

Topical nasal antihistamines, such as azelastine, are also available and are recommended for nasal-limited mild disease and for on-demand treatment.[10] To augment the efficacy of oral antihistamines in allergic rhinitis for those who continue to have symptoms, the preferred topical therapy is a corticosteroid nasal spray. These sprays should be considered first-line treatment in moderate to severe allergic rhinitis.[10] Combination treatments containing both corticosteroids and antihistamines are also available. Adjunctive treatments such as intranasal ipratropium bromide may be useful in reducing rhinorrhoea in those with perennial allergic rhinitis[11] while nasal irrigation using saline solution may improve symptoms and reduce the need for oral antihistamines.[12]

Allergic conjunctivitis

Like allergic rhinitis, allergic conjunctivitis is IgE-mediated. It can be seasonal due to pollens or perennial due to allergens present all year.[13] Seasonal allergic conjunctivitis is typically associated with some degree of allergic rhinitis so allergen avoidance is the first step in management.

Oral antihistamines can be used for allergic conjunctivitis or, if the symptoms are only related to the eye, topical antihistamines with or without mast cell stabilisers are recommended.[13] Some topical products such as ketotifen, azelastine and olopatadine have both antihistamine and mast cell stabilising effects. Mast cell stabilisers such as sodium cromoglycate are also available. Topical antihistamines give immediate relief, while mast cell stabilisers provide more long-term protection.[13]

The current guidelines for ocular-limited disease are either topical antihistamines, mast cell stabilisers or dual action drugs.[13] A Cochrane review has shown that both antihistamines and mast cell stabilisers are more effective than placebo for seasonal and perennial allergic conjunctivitis, however there have been no good studies to compare mast cell stabilisers to antihistamines.[14]

Acute allergic reactions

The newer H_1 antihistamines are the mainstay treatment of mild to moderate allergic reactions giving rise to allergen-specific mast cell degranulation. Patients with a known food allergy are advised to carry these less sedating H_1 antihistamines as part of their allergy action plan. The use of sedating antihistamines should be avoided, especially because their sedative effects may mask a deterioration in consciousness, caused by the underlying allergic reaction, indicating the onset of anaphylaxis and the requirement for adrenaline (epinephrine).

Antihistamines have no role in the acute treatment of anaphylaxis because intramuscular adrenaline (epinephrine) must be given. Parenteral antihistamines can potentiate hypotension and worsen anaphylaxis.[15] Once the acute anaphylaxis has been treated, less sedating antihistamines and steroids may be used for symptomatic relief of urticaria.

Urticaria

In about 50% of cases, acute urticaria is not due to IgE-mediated mast cell degranulation, but occurs as a result of direct mast cell degranulation from spontaneous activation or infection. In children, the most common cause of urticaria is infection rather than IgE-mediated allergic reactions.

Irrespective of the cause of the urticaria, the less sedating antihistamines are the mainstay of the treatment. A failure of the rash to clear with these antihistamines (even if only temporarily) should prompt re-evaluation of whether the rash is truly urticarial.

Chronic spontaneous urticaria is a long-term condition of spontaneous mast cell degranulation and may occur in conjunction with various forms of physical urticaria caused by exposure to:

- water (aquagenic)
- sweat (cholinergic)
- sun (solar)
- cold
- prolonged pressure (delayed pressure urticaria).

These patients may display dermatographism. This is welting of the skin after a scratch or gentle pressure.

For patients with physical urticaria, the newer antihistamines can be used for treatment or for prophylaxis. They sometimes require up to four times the recommended dose for this treatment.

The less sedating H_1 antihistamines are also the mainstay of treatment for chronic spontaneous urticaria. This is defined by the appearance of hives at least a few times a week for more than six weeks.[16] Antihistamines are most effective when dosed regularly (twice a day) to prevent the onset of hives, rather than waiting for their appearance. If required, antihistamines can be used at up to four times the recommended dose.[16,17] If H_1 antihistamines are not effective at this dose, H_2 antihistamines such as ranitidine and famotidine (which block the H_2 receptors found in the stomach, vascular smooth muscle and elsewhere) can be added.[2] They are given twice a day with the same total dose as for gastroeosophageal reflux. H_2 antihistamines do not help urticaria on their own, but can augment the effect of H_1 antihistamines.

Chronic spontaneous urticaria is a relapsing, remitting disease which may spontaneously improve. Patients are therefore encouraged to decrease or stop their antihistamines intermittently to ensure that the drugs are still required. Chronic spontaneous urticaria can be an autoimmune disease.[17] It can also be a marker of other underlying autoimmune diseases, particularly thyroid autoimmunity, so patients should be assessed to exclude associated conditions.

Colds and flu

There is no role for antihistamines for cold and flu symptoms.

Prevention of motion sickness

Cyclizine is a sedating antihistamine used specifically for prevention of motion sickness. Other sedating antihistamines such as promethazine can also be used to treat nausea and vomiting from motion sickness.

Tachyphylaxis

There is a widespread belief in the community that taking long-term antihistamines makes them less effective and that it is better to swap between different types of antihistamines for the best effect. There is no compelling evidence that tachyphylaxis occurs with the newer H_1 antihistamines.[1] A recommendation to swap treatment is not contained in any of the position statements of the major societies which provide advice about antihistamine use. Multiple studies have shown that the effectiveness of the newer drugs in ameliorating the effect of histamine release in the skin continues unchanged for up to 30[18] to 180 days.[19]

Patients may mistake an intensification of the underlying symptoms for a waning in effectiveness of the antihistamine. There are situations in which a pre-emptive intensification of treatment may be required – such as before contact with a known trigger or in the weeks before the onset of the spring pollen season. However, this intensification of treatment can be achieved by increased doses of the patient's usual antihistamine and does not need to involve a change to a new antihistamine that may cause idiosyncratic reactions.

Adverse effects and overdose

Newer, less sedating antihistamines have very few adverse effects. Cetirizine is the one most likely to cause sedation,[20] particularly in higher doses. Although very rare, idiosyncratic hypersensitivity reactions have been described for each of the antihistamines. Other reported adverse effects are headache, fatigue, drowsiness, insomnia and rash.

Sedating antihistamines have been associated with a lowered seizure threshold. Reports of seizures in patients taking less sedating antihistamines have been received by medicine safety authorities, but the causal link with the antihistamines has not been confirmed.[21]

Overdoses of newer, less sedating antihistamines may result in tachycardia, drowsiness, agitation, gastrointestinal effects and headache. An ECG is recommended. Overdoses of sedating antihistamines can give rise to dangerous sedation as well as anticholinergic signs. Seizures and cardiac conduction abnormalities may also occur.[22]

Conclusion

Antihistamines are effective at relieving the itch caused by the release of histamine. They have a role in treating allergic rhinitis, allergic conjunctivitis and urticaria. The older antihistamines caused sedation so they have now been superseded by newer, less sedating drugs. ≺

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Antihistamines are mast cell stabilisers.
2. Oral antihistamines are the first-line management for allergic conjunctivitis.

Answers on page 57

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ARTICLE

Safer dispensing labels for prescription medicines

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SUMMARY

The standard way in which directions are represented on dispensing labels can be misinterpreted.

Errors in interpreting instructions are more common in people with low health literacy and when the timing of administration is not specified.

Improving written communication on prescriptions and dispensing labels can reduce medication errors.

There is an emerging international consensus on best-practice communication on dispensing labels.

Introduction

Dispensing labels on prescribed medicines provide administration instructions and important warnings. These remain with the consumer after the initial consultation when some of the confusion and worry frequently associated with illness has started to recede. Incorrect information on a label can have disastrous consequences,[1] but even correct information can contribute to medication errors.

An *Australian Prescriber* report described three cases of paediatric dosing errors involving prednisolone.[2] In each case, parents administered prednisolone three times a day rather than daily as intended. While the directions on the label appeared to be correct – for example 'give 3 mL daily after food for three days' – they were misinterpreted. Research has found these types of errors are relatively common and can be reduced by better communication on dispensing labels.[3,4]

Health literacy

Health literacy refers to the ability of individuals to access, understand and use information to maintain good health. There are two components to health literacy – individual health literacy and the health literacy environment. Individual health literacy refers to an individual's skills, knowledge and capacity to access, understand and act on health information, and the health literacy environment refers to the ways in which the health system affects the ability of someone to access, understand and use information to maintain their health.[5] Improving the written communication on dispensing labels is a good example of how improving the health literacy environment can improve patient care.

Medication errors

In a US trial, 395 participants were given five common prescription medicines with a dispensing label and asked how they would take the medicine.[4] The medicines and their instructions included:

- amoxicillin, 'take one teaspoonful by mouth three times a day'
- furosemide (frusemide), 'take one tablet in the morning and one at 5 pm'
- guaifenesin, 'take two tablets by mouth twice daily'.

Almost half of the participants misunderstood one or more of the dispensing labels. Errors were more common in those with low health literacy (reading ability of sixth grade or less) and when less explicit directions were provided. For instance, 41.3% of participants with low health literacy misunderstood the directions for amoxicillin, whereas only 17.3% of the participants with low health literacy misunderstood the more explicit directions for furosemide (frusemide). A separate analysis of the same study showed that errors in relation to the amoxicillin directions were a mixture of misunderstanding the measurement of the dose and the timing of administration. For example 'take one teaspoonful by mouth three times a day' was misunderstood as 'take three teaspoons daily' or 'take three tablespoons every day'.[6]

Having someone accurately describe the dose of a medicine does not mean that they will take the correct dose. Participants were asked how many guaifenesin tablets they would take each day when instructed to 'take two tablets by mouth twice daily'.[4] Some participants who could appropriately describe the recommended dose still made an error when asked to demonstrate how many tablets they would

take in a day. This occurred in people with both high and low health literacy. However, in those with high health literacy, 89.4% correctly described the dose and 80.2% correctly demonstrated the number of tablets to be taken daily. For participants with low health literacy, 70.7% correctly described the dose but only 34.7% correctly demonstrated the daily dose.

In the same trial, participants interpreted 'take two tablets by mouth twice daily' in a variety of ways.[6] Interpretations included 'take one tablet every 8 hours', 'take one tablet every 12 hours' and 'take tablets every day'. Adding details about the duration of treatment led to further variation in how people interpreted directions. Some participants omitted information about duration from their understanding of the directions, others mentioned duration at the expense of information regarding the number of tablets or interval. For instance, some people interpreted 'take two tablets twice a day for 7 days' as 'take it for 7 days' or 'take one every day for a week'.

These findings provided an impetus for re-thinking how information is communicated on dispensing labels.

Patient-centred labels

There is an emerging consensus for communicating less confusing, more informative and safer information on dispensing labels.[7–9] These labels have been called patient-centred labels, and recommendations have been developed based on research in health literacy and health communication (see Box 1).[3,10,11] Advice includes:

- use larger font sizes (e.g. 12 point and above)
- present complex information in lists rather than paragraphs when possible
- use numbers rather than words to convey numeric information, for example 'take 2 tablets…' rather than 'take TWO tablets…'
- provide explicit dosing instructions, for example 'take 2 tablets in the morning, and take 2 tablets in the evening' rather than 'take TWO tablets TWICE a day'
- use white space and typographical cues (e.g. capitals) to communicate important information
- use standard dosing times for medicine administration, for example 'morning, noon, evening, bedtime' rather than 'TWICE daily', 'FOUR times daily' or 'every SIX hours'
- include the indication for the medicine when possible.

The use of standard dosing times, 'morning, noon, evening, bedtime', has been labelled the 'universal medication schedule'.[10,12] The use of standard dosing times is feasible for most drugs and is less confusing, more informative and makes it easier for patients to consolidate multiple medicines into fewer dosing times throughout the day.[4,9]

How effective are patient-centred dispensing labels?

A number of studies have assessed patient-centred labels.[12–14] One trial randomised 845 participants to receive a patient-centred label or standard dispensing label for their medicine.[12] The study assessed whether participants could show appropriate use of the medicine at baseline, three months and nine months. 'Appropriate use' meant the participant could report how many tablets or capsules per dose, how many times the medicine needed to be taken per day, and the total number of tablets or capsules to be taken per day. Those who received patient-centred labels were better at describing their medicine use at baseline (nominally) and at nine months compared with those who received standard dispensing labels (76.9% vs 70.1%, p=0.06 at baseline, 85.9% vs 77.4%, p=0.03 at 9 months). There was no difference between the groups at three months.

This study included participants who were fluent in either English or Spanish. Spanish-speaking participants did not receive the same benefit from patient-centred labels that was observed in English-speaking participants.[12] This finding highlights the importance of further research in the use of patient-centred labels in patients from non-English speaking backgrounds. Most of the studies to date have excluded people who do not speak English.

Box 1 Proposed standards for patient-centred labels

Use explicit text to describe the dose and the administration interval in instructions.

Use a universal medication schedule to convey and simplify instructions for dosing or use, i.e. provide instruction to take medicine at standard dosing times 'morning, noon, evening, bedtime'.

Include distinguishable front and reverse sides to the label.

When possible, include indication for use.

Simplify language, avoiding unfamiliar words or medical jargon.

Improve typography, use larger sans serif font.

When applicable, use numeric rather than alphabet characters.

Use typographic cues (bolding and highlighting) for patient content only.

Use horizontal text only.

Use a standard icon system for signalling and organising auxiliary warnings and instructions.

Adapted from Reference 10.
Australia has a national 'standard icon system' for cautionary advisory labels. See the Australian Pharmaceutical Formulary and Handbook for a full list.[11]

Medication adherence

The study comparing patient-centred labels with standard dispensing labels also assessed medication adherence.[12] While there was no difference in adherence in the groups overall, participants with low health literacy who received patient-centred labels were more likely to adhere to their medicine than those who received standard labels.

The Australian context

Almost 60% of Australian adults have low health literacy.[5] It is easy for health professionals to underestimate the workload expected of consumers in managing their care and the care of family members.[15,16] Patient-centred labels improve the healthcare environment by helping people to manage their medicines. They are an important addition to the face-to-face communication that occurs in consultations between the consumer and prescribers, pharmacists and other health professionals.

Guidelines

The specific legislative requirements for dispensing labels provided by pharmacists, prescribers, nurse practitioners and dentists are defined in state-based regulations and are informed by the Poisons Standard.[17] The Pharmacy Board of Australia's Guidelines for Dispensing of Medicines provides best-practice guidance for the labelling of dispensed medicines (this guidance does not currently include specific recommendations for patient-centred labels).[18] Box 2 provides Pharmacy Board of Australia guidance regarding the content that should be included on the label of a dispensed medicine.[18]

Box 1 provides guidance for patient-centred labels developed by the US Institute of Medicine.[10] Similar guidance has been issued locally and internationally.[7-9] The Australian Commission on Safety and Quality in Health Care is currently developing national standards for pharmacy dispensing labels. National standards are essential to guide practice and inform collaborative efforts to improve communication on dispensing labels. Challenges include deciding how best to implement the recommendations in Australia as labelling practices differ internationally and key studies have implemented patient-centred labels in slightly different ways. Also, making the necessary changes to prescribing and dispensing software and associated support systems will be a major undertaking, and further research is needed to ensure the effectiveness of patient-centred labels for people from non-English speaking backgrounds.

It is also possible that label dimensions need review. Currently it is difficult to present even relatively simple directions in a sufficient font size with surrounding white space to aid readability. The Table provides examples of common instructions provided in a way that implements the recommendations for patient-centred labels.[12-14,19]

While there is work to be done to ensure patient-centred labels are implemented in Australia in a safe and effective manner, some aspects can be implemented immediately. Prescribers should, when possible, avoid 'as directed' and provide the indication. They should also give dosing directions at standard dosing times. If possible, pharmacists should provide explicit directions using standard dosing times, align warning labels horizontally, and discuss the inclusion of the indication on the dispensing label with the consumer.

Box 2 What should be included in a medicine label?

Brand and generic names of the medicine, and the strength, dose form and quantity supplied

Specific directions for use, including frequency and dose

Patient's name

Date of dispensing or supply

Initials of the dispensing pharmacist (and if different, the initials of the pharmacist checking and issuing the medicine)

Name, address and telephone number of the dispensing pharmacy

Storage directions and expiry date of the medicine

The words 'Keep out of reach of children'

Based on the Pharmacy Board of Australia's Guidelines for Dispensing of Medicines. Refer to the Guidelines for the Board's full list.[18]

Table Examples of instructions on medicine labels

Drug	Standard instructions	Patient-centred instructions
Metformin tablets 500 mg	Take TWO tablets TWICE a day	Take 2 tablets in the morning 2 tablets in the evening Take for diabetes
Prednisolone oral liquid 5 mg/mL	Give THREE mL by measure daily for THREE days	For 3 days: Give 3 mL in the morning for asthma
Paracetamol 500 mg	Take ONE to TWO tablets every FOUR to SIX hours if necessary. (Maximum 8 tablets in 24 hours)	If you have pain, Take 1 or 2 tablets. Wait at least 4 hours before taking again. Do not take more than 8 tablets in 24 hours.

Source: References 12-14, 19

Conclusion

What is considered best practice for dispensing labels is changing. Implementing these recommendations will require changes in prescribing and pharmacy practice and their support systems. Improving communication on dispensing labels helps consumers to safely manage their medicines and is an important addition to specific verbal advice on medication use. ◀

Conflict of interest: none declared

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ARTICLE

Pharmacovigilance and expedited drug approvals

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SUMMARY

Pharmacovigilance is the detection and assessment of adverse events related to any drug used in clinical practice.

In Australia adverse events can be reported to the Therapeutic Goods Administration. Reports are encouraged, even if the drug is old or the prescriber is only suspicious of an adverse event.

Australian information about adverse events can be found online in the Database of Adverse Event Notifications and in the publication Medicine Safety Update.

The Therapeutic Goods Administration is currently exploring expedited approval pathways to enable some drugs to reach the market quickly. As there will be limited clinical data about these drugs, postmarketing pharmacovigilance will be of increased importance.

Introduction

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[1] Most reporting of adverse effects occurs after a drug is marketed. Postmarketing pharmacovigilance is essential as adverse events often only become apparent after a drug enters clinical practice. Premarket clinical trials are limited by short duration and small sample sizes. The patients are tightly selected, with strict inclusion and exclusion criteria. This limits the power of the trials to detect adverse events that occur rarely, after a protracted period of time, or in patients who are different from the study population.

Pharmacovigilance in Australia

Pharmacovigilance formally began in Australia in 1963, as a response to reports of thalidomide embryopathy, with the formation of the Australian Drug Evaluation Committee. Despite multiple policy and committee name changes, data on adverse events have been collected constantly since then. As of January 2017, the Advisory Committee on Medicines, a subcommittee of the Therapeutic Goods Administration (TGA), is responsible for pre- and postmarketing surveillance, including pharmacovigilance.

In the past, adverse events were reported to the TGA by the submission of a 'blue card'.[2] These cards are no longer available in a physical form. Clinicians can now notify the TGA of adverse events via the online Australian Adverse Drug Reactions Reporting System.[3] Alternatively reports can be made via telephone, post, fax and email. Anyone, including the general public (on a separate online consumer portal), can report adverse events to the TGA.

A report can be made even if there is only a suspicion of a drug causing an adverse effect. It is the TGA's responsibility to investigate and determine causality. Ideally, all adverse events should be reported, but the TGA is most interested in those events listed in Box 1. Reporting already known or common adverse events helps the TGA continue to build the 'safety profile' of a drug.

Reporting by clinicians and the general public is voluntary. In contrast, sponsors of both registered and listed drugs are legally mandated to report to the TGA all suspected adverse events they receive or become aware of from any source, even if the sponsor does not agree that there is causality. In 2015, the TGA received 17 000 reports with 54% coming from sponsors and 15% from state and territory health departments (reporting adverse

Box 1 Adverse events of particular interest to the Therapeutic Goods Administration

Adverse event related to newly listed or registered drugs

Adverse event related to medicine or vaccine interactions

Suspected adverse event not listed in product information or in medical resources

Adverse event leading to death, admission to hospital, prolonged hospitalisation or birth defects

events following immunisations). Only 4% of the reports came from GPs.[4] From a quality perspective, not all reports may be considered equal, with sponsor reports more likely to lack important causal and correlative data.[5]

All data reported to the TGA are entered into the Australian Adverse Drug Reactions Reporting System. Data are also submitted to VigiBase, the World Health Organization's international database of adverse drug events. These databases are analysed to detect signals which may identify previously unrecognised safety problems, an increased frequency or severity of adverse events, or patient groups that are particularly sensitive to adverse events.

Adverse event data reported to the TGA since 1971 are publically available through the online Database of Adverse Event Notifications, established in October 2012. It is important to be aware that this database does not contain all known adverse events and cannot be used to determine adverse event rates. Clinicians can also obtain information on emerging safety concerns and adverse events in the publication Medicines Safety Update[6] or via TGA alerts. VigiAccess is the online access point for international data submitted to VigiBase (vigiaccess.org).

Australian reporting has led to the early recognition of adverse events. Examples include the risk of liver failure from lumiracoxib,[7] black cohosh[8] and flucloxacillin,[9] and acute kidney injury from the 'triple whammy' (combination of ACE inhibitor, non-steroidal anti-inflammatory and diuretic).[10] Recently, reporting identified the risk of QT prolongation with denosumab.[11] The Table highlights other significant safety issues noted by the TGA since 2010.

Further information on Adverse Event Reporting is freely available through the NPS MedicineWise module 'Safety through Adverse Event Reporting' at www.nps.org.au/cpd/activities/safety-through-adverse-event-reporting.

Limitations

There are significant limitations with Australian adverse event reporting. Like other methods of observational research, the lack of a known sample size limits the ability to determine the rate of events. The numerator is also highly dependent on reporting by clinicians and the general public. Voluntary reporting leads to significant under-reporting of adverse events. In the UK it estimated that reports probably represent less than 10% of actual events.[12] Furthermore, only basic demographics are collected by the TGA (Box 2). No comorbidity data are available. These factors limit the ability to determine contributory and confounding factors to an adverse event.

Pharmacovigilance and expedited approvals

A review of medicines and medical device regulation in 2015 has recommended that the TGA implement expedited pathways for promising new drugs.[13] This would enable the TGA to grant provisional approval of a new drug on the basis of early data, if the immediate availability of the drug outweighs the risk that additional data are still required. Similar pathways currently operate in Europe, Canada and the USA.[14]

In response to the review, the TGA released two consultation papers in 2017. The first aimed to seek opinions on enhancements to the current Medicines Vigilance Framework in order to better identify and address medicine safety concerns.[15] Specifically, the Black Triangle Scheme, similar to that already operating in Europe, will be introduced to identify newly available drugs requiring increased vigilance. This will alert clinicians and consumers that these drugs are subject to additional monitoring and prompt them to report adverse events to the TGA. This may improve the rate of reporting in the postmarketing phase to help identify rare adverse events. Changes are also being proposed for the product information to improve the accessibility of prescribing information.[15]

The second paper asked for discussion of a provisional approval pathway.[16] This pathway is designed to permit the clinical use of 'promising' medicines for patients with unmet clinical needs earlier than would normally be allowed. Provisional approval would be granted with significantly less clinical data than currently required. Decisions are likely to be made before phase III trials have been designed. This is important as many clinical trials fail from lack of efficacy, safety concerns, or a combination.[17] Other phase III trials may meet the primary end point, but find mortality is worse, as seen with evolocumab and fibrates.[18,19]

In order to obtain full registration, sponsors must submit confirmatory data on efficacy and safety. However, there is the real possibility that a promising drug is never given full approval because subsequent trials do not confirm a benefit. By then the drug may have been used in clinical practice for up to two years under provisional approval. Increased pharmacovigilance will therefore be essential for these new drugs.

Safety concerns

Bypassing the traditional premarket approval process moves the experimentation phase of drug development into the real world. Under provisional approval, drugs will be applied in clinical practice before their comparative safety and efficacy are known and without the stringent follow-up and protection afforded by clinical trials. While there will

Table **Examples of adverse events reported to the Therapeutic Goods Administration**

Drug	Adverse event
Sodium glucose co-transporter 2 inhibitors	Diabetic ketoacidosis (atypical presentation)
Risperidone	Cerebrovascular events in patients with dementia
Infliximab	Non-melanoma skin cancers (particular in psoriasis)
Methotrexate	Hepatitis B reactivation
Non-steroidal anti-inflammatory drugs (over-the-counter doses used for prolonged periods)	Cardiovascular events Diclofenac – hepatotoxicity
Combined oral contraceptives and hormonal replacement therapy	Potential link with inflammatory bowel disease
Metoclopramide	Extrapyramidal events and cardiac conduction – new recommendations for prevention
Pregabalin	Suicidal ideation
Zolpidem	Next day impairment
Duloxetine	Serotonin syndrome
Rotavirus vaccine	Intussusception
Denosumab	Severe hypocalcemia
Proton pump inhibitors	Acute interstitial nephritis
Clozapine	Constipation
Exenatide	Pancreatitis

be increased emphasis on pharmacovigilance in the provisional pathway, including random audits, these mechanisms have not yet been fully scrutinised and may not provide enough protection for patients.

Sponsors are legally mandated to report all negative outcomes they become aware of, but there is no imperative for them to actively search for adverse events. As reporting by clinicians will remain voluntary it is likely that there will be significant under-reporting of adverse reactions to provisionally approved drugs. However, adverse events from specialist-only drugs such as immunotherapies may have a higher rate of detection and reporting due to hospital reporting systems.

Postmarketing safety concerns have been raised with the provisional approval process implemented in Canada, a process similar to that proposed in Australia. There is a statistically significant risk that drugs approved under this mechanism will receive a serious safety warning or be removed from market compared to those approved by a standard review process.[20]

Despite these concerns we are still not entirely certain how the provisional approval pathway will be implemented in Australia by the TGA. At present, the TGA is yet to announce its complete plans for monitoring the safety and efficacy of these provisionally approved drugs. The TGA already has the power to impose conditions on the registration of a new drug. For example, an existing condition of registration of new drugs has been the requirement for a risk management plan.[21] The TGA will undertake monitoring to ensure the contents of these plans, such as collecting additional safety data, are carried out.[15]

Box 2 **Data collected by the Therapeutic Goods Administration**

Basic patient demographics (sex, date of birth or age, weight, ethnicity, state)

Drug details (dose, frequency, form, route, date started, date stopped, indication, batch number)

Adverse reaction (date of onset, description, severity, treatment, outcome, sequelae)

Reporter details (name and address)

Optional supporting documentation

Future proposals

The reason for the development of the TGA and its safety committees was to ensure safety and monitor new therapies in clinical practice. Patient protection is key if drugs are to be used in an experimental manner. In addition to the

proposed pharmacovigilance measures in the provisional approval pathway, there could be a drug registry in order to prevent harm. This registry could be established and managed by pharmacoepidemiologists and linked research groups working with the TGA. Prescribers using provisionally approved drugs would be required to enter patient data on safety and outcomes into the register. Provisionally approved drugs could be identified in prescribing software, product information and in medicine resources through the TGA's Black Triangle Scheme. In this way serious adverse events and lack of efficacy would be identified early.

Conclusion

A balance between experimentation and the rapid provision of promising new drugs for serious or life-threatening conditions is needed. Pharmacovigilance will be of increasing importance if drugs are approved for use on the basis of limited trial data.

Jennifer Martin has contributed to the Therapeutic Goods Administration consultation processes as an employee of the University of Newcastle and as a member of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists.

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ANAPHYLAXIS WALLCHART

Anaphylaxis: emergency management for health professionals

Aust Prescr 2018;41:54
https://doi.org/10.18773/austprescr.2018.014

Download an A3-sized poster of the Anaphylaxis Wallchart (updated 2022).

Order your FREE laminated A3-sized copy of the Anaphylaxis Wallchart 2022 from the NPS ordering portal.

Updated 5 May 2022

This is the most up-to-date version (v2) of the wallchart.

Update notice available at: https://doi.org/10.18773/austprescr.2022.022

Australian Prescriber

Anaphylaxis: emergency management for health professionals

Clinical features

Any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, **even if typical skin features are not present**

OR

Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema) **PLUS** Involvement of respiratory, cardiovascular, or persistent severe gastrointestinal symptoms

1 Immediate action

- Call for assistance
- Lay the patient flat – do not allow them to stand or walk.
  If unconscious or pregnant, place in recovery position (left lateral if pregnant) and maintain airway.
  If breathing is difficult, allow the patient to sit with legs outstretched.
  Hold young children flat, not upright.

2 Give INTRAMUSCULAR ADRENALINE (EPINEPHRINE) into mid-lateral thigh without delay

Adrenaline dose chart (1:1000 ampoules containing 1 mg adrenaline per 1 mL)

Age (years)	Weight (kg)	Adrenaline volume 1:1000
<1	5–10	0.05–0.1 mL
1–2	10	0.1 mL
2–3	15	0.15 mL
4–6	20	0.2 mL
7–10	30	0.3 mL
10–12	40	0.4 mL
>12 and adult	>50	0.5 mL

Autoinjector

An adrenaline autoinjector, e.g. EpiPen or Anapen, may be used instead of an adrenaline ampoule and syringe.

- 150 microgram (0.15 mg) device for children 7.5–20 kg (aged ~1–5 years)
- 300 microgram (0.3 mg) device for children over 20 kg (aged ~5–12 years) and adults
- 300 microgram (0.3 mg) or 500 microgram (0.5 mg) device for children over 50 kg (aged ~ >12 years) and adults

Instructions are on device labels and ASCIA Action Plans.

Repeat adrenaline every 5 minutes as needed
If multiple doses are required, consider adrenaline infusion if skills and equipment available (see step 5).

Remove allergen (if still present): flick out insect stings, freeze ticks with liquid nitrogen or ether-containing spray (if available) and allow to drop off.
ALWAYS give adrenaline FIRST, then asthma reliever puffer, if someone with known asthma and allergy to food, insects or medicine has SUDDEN BREATHING DIFFICULTY (including wheeze, persistent cough or hoarse voice) even if there are no skin symptoms.

3 Call ambulance to transport patient to hospital

Keep the patient flat and transfer to ambulance via stretcher. Do not allow them to stand or walk even if they appear to have recovered following administration of adrenaline.

4 Supportive management

When skills and equipment are available:

- monitor pulse, blood pressure, respiratory rate, pulse oximetry
- give oxygen and airway support if needed
- obtain intravenous access in adults and hypotensive children
- if hypotensive, give intravenous normal saline (20 mL/kg rapidly) and consider additional wide-bore intravenous access.

5 Additional measures

Adrenaline (epinephrine) infusion

If inadequate response or deterioration, start an intravenous adrenaline infusion as follows:
Give only in liaison with an appropriate specialist. Phone .....

- Mix 1 mL of 1:1000 adrenaline in 1000 mL of normal saline
- Start infusion at 5 mL/kg/hour (0.1 microgram/kg/min)
- Titrate rate according to response
- Monitor continuously

If adrenaline (epinephrine) infusion is ineffective or unavailable, also consider:

For upper airway obstruction

- nebulised adrenaline (5 mL, i.e. 5 ampoules of 1:1000)
- intubation if skills and equipment are available

For persistent hypotension/shock

- give normal saline (maximum 50 mL/kg in the first 30 min)
- in patients with cardiogenic shock (especially if taking beta blockers) consider an intravenous glucagon bolus of 1–2 mg in adults (in children: 20–30 micrograms/kg up to 1 mg). This may be repeated or followed by an infusion of 1–2 mg/hour in adults
- in adults, selective vasoconstrictors metaraminol (2–10 mg) or argipressin (vasopressin) (10–40 units) only after advice from an appropriate specialist

For persistent wheeze

- bronchodilators: salbutamol 8–12 puffs of 100 micrograms using a spacer or 5 mg salbutamol by nebuliser
- oral prednisolone 1 mg/kg (maximum 50 mg) or intravenous hydrocortisone 5 mg/kg (maximum 200 mg)

6 Observation

Prolonged and biphasic reactions may occur.

Observe the patient for at least 4 hours after last dose of adrenaline.

Observe longer (overnight) if the patient:

- had a severe reaction (hypotension or hypoxia), or
- required repeated doses of adrenaline, or
- has a history of asthma or protracted anaphylaxis, or
- has other concomitant illness, or
- lives alone or is remote from medical care, or
- has known systemic mastocytosis.

Document food, medicine, sting/bite exposure in the 2–4 hours before anaphylaxis.

7 Follow-up treatment

Corticosteroids

The role of corticosteroids is unknown. It is reasonable to prescribe a 2-day course of oral steroid (e.g. prednisolone 1 mg/kg, maximum 50 mg daily) to reduce the risk of symptom recurrence after a severe reaction or a reaction with marked or persistent wheeze. Corticosteroids should only be administered after adrenaline and resuscitation.

Adrenaline (epinephrine) autoinjector

Prescribe an autoinjector, pending specialist review. Train the patient in autoinjector use and give them an ASCIA Action Plan for Anaphylaxis - www.allergy.org.au.

Allergy specialist

Refer patients with anaphylaxis for review.

Antihistamines

Antihistamines have no role in treating respiratory or cardiovascular symptoms of anaphylaxis. Oral non-sedating antihistamines treat itch and urticaria. Injectable promethazine should NOT be used in anaphylactic shock as it can worsen hypotension.

Originally published in the April 2018 edition of *Australian Prescriber* (vol. 41, no. 2), and updated in 2022. https://doi.org/10.18773/austprescr.2018.014
Endorsed by the Australasian College for Emergency Medicine, the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, the Australasian Society of Clinical Immunology and Allergy (ASCIA), the Australian College of Rural and Remote Medicine, the Australian Dental Association, the Internal Medicine Society of Australia and New Zealand, and the Royal Australasian College of Physicians.
This Anaphylaxis Wallchart has been officially recognised as an Accepted Clinical Resource by the Royal Australian College of General Practitioners.

New drugs

Avelumab

Approved indication: Merkel cell carcinoma

Bavencio (Merck)
vials containing 200 mg/10 mL for dilution
Australian Medicines Handbook section 14

The Therapeutic Goods Administration has an orphan drug program to encourage pharmaceutical companies to market treatments for rare conditions in Australia. Avelumab is an immune checkpoint inhibitor that has been designated as an orphan drug for the treatment of metastatic Merkel cell carcinoma. This is a rare form of skin cancer but, due to an association with ultraviolet radiation, Australia has the highest incidence in the world (1.6/100 000 people). The cancer is also associated with immunosuppression and Merkel cell polyomavirus. It presents as a rapidly growing painless nodule and has a poor prognosis. Patients can be given chemotherapy, but the median progression-free survival is only about two months. The mortality rate is higher than that of melanoma and patients with metastatic Merkel cell carcinoma only have a median survival of 9.6 months.

Avelumab acts against cancer cells by altering the immune response. Some cancer cells express a protein called programmed cell death ligand 1. This reduces the activity of T-lymphocytes against the tumour. Avelumab is a monoclonal antibody that binds to the ligand preventing it from binding to its receptor. This encourages reactivation of the immune response to cancer cells.

The drug has to be diluted and given by slow intravenous infusion. It is catabolised like other proteins. The half-life is six days, but clearance may decrease during treatment. Renal disease has no significant effect, but the effect of severe hepatic impairment on the drug's pharmacokinetics is unknown.

In Australia the approval of avelumab for Merkel cell carcinoma is based on one uncontrolled, open-label, phase II study. This enrolled 88 patients who had already been treated for metastatic disease. They were given infusions at a dose of 10 mg/kg every two weeks and assessed by the Response Evaluation Criteria in Solid Tumours. The median duration of treatment was 17 weeks and the median follow-up was 10.4 months.[1]

The primary outcome of the trial was the overall response to treatment. Eight patients had a complete response and 20 had a partial response giving an overall response rate of 31.8%. At six months, 69% of the patients were still alive. The median overall survival was 11.3 months.[1]

Treatment-related adverse events affected 70% of the patients. Some adverse effects are the predictable consequences of infusing a drug that alters the immune system. These include immune-mediated pneumonitis, hepatitis, nephritis, colitis and endocrinopathies. Infusion reactions are common and premedication with antihistamines and paracetamol is recommended. Other frequent adverse reactions include fatigue, peripheral oedema, musculoskeletal pain, diarrhoea, nausea and anaemia. Avelumab should be avoided in pregnancy and lactation because of its potential for harm.

Another immune checkpoint inhibitor pembrolizumab has also shown some efficacy in Merkel cell carcinoma, so this class of drugs may have an increasing role in treatment. However, in the phase II trial of avelumab only a minority of the 88 patients responded and 43 patients died, with most of these deaths being due to progressive disease. Median progression-free survival was 2.7 months.[1] As the trial excluded patients with significant comorbidities or immunosuppression, avelumab will not be suitable for all patients. Further research will reveal whether avelumab is effective earlier in the course of the disease.

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

Aust Prescr 2018;41:55
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First published 27 February 2018

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

Aust Prescr 2018;41:56–7
https://doi.org/10.18773/austprescr.2018.019
First published 27 February 2018

Carfilzomib

Approved indication: multiple myeloma

Kyprolis (Amgen)
vials containing 30 mg and 60 mg powder
Australian Medicines Handbook section 14.1.8

Carfilzomib is a new intravenous drug for multiple myeloma. It is indicated for people with relapsed or refractory disease after at least one previous therapy. It should be given in combination with dexamethasone or with lenalidomide and dexamethasone.

Like bortezomib, carfilzomib is a proteasome inhibitor. It works by interfering with the system for breaking down proteins within cells. As cancer cells are rapidly multiplying, inhibiting proteasomes causes proteins to accumulate. In in vitro and animal studies, this slows cell growth and eventually causes cell death.

The approval of carfilzomib is based on two randomised open-label trials – ASPIRE[1] and ENDEAVOR.[2] The trials enrolled people who had been treated with 1–3 previous therapies.

In the ASPIRE study, carfilzomib with lenalidomide and dexamethasone was compared to lenalidomide and dexamethasone alone for 18 treatment cycles. Patients who had previously progressed on bortezomib or lenalidomide with dexamethasone, or had previously discontinued lenalidomide and dexamethasone because of an adverse effect, were not allowed in the trial.[1]

The progression-free survival of patients was longer when carfilzomib was added to lenalidomide and dexamethasone compared with those given lenalidomide and dexamethasone alone (26.3 vs 17.6 months, p=0.0001). Also more patients in the carfilzomib arm had at least a partial response to treatment (87.1 vs 66.7%, p<0.001) (see Table).

Diarrhoea (42.3% vs 33.7%), thrombocytopenia (29.3% vs 22.9%), cough (28.8% vs 17.7%), fever (28.6% vs 20.8%), upper respiratory tract infection (28.6% vs 19.5%), hypokalaemia (27.6% vs 13.4%), hypertension (14.5% vs 7.5%), and headache (13.5% vs 8%) were more common with carfilzomib than with the comparator.[1]

In the ENDEAVOR study, carfilzomib plus dexamethasone was compared to bortezomib plus dexamethasone. Although patients who had previously been treated with carfilzomib or bortezomib were allowed in the trial, they must have had at least a partial response to the treatment before relapse and not discontinued because of an adverse effect.[2]

As in the ASPIRE trial, progression-free survival was significantly longer in the carfilzomib arm compared with the comparator (18.7 vs 9.4 months, p<0.0001). Overall response rates were also higher (76.9 vs 62.6%, p<0.0001) (see Table).[2]

Anaemia (40.8% vs 27.6% of patients), fever (31.3% vs 14.7%), dyspnoea (30.5% vs 13.2%), hypertension (29.8% vs 9.6%), cough (26.1% vs 14.9%), muscle spasms (19.7% vs 6.1%), and bronchitis (21.4% vs 10.1%) were more frequent with carfilzomib than with bortezomib.[2]

Cardiac failure (7%) was reported with carfilzomib in the trials, as was myocardial infarction (2%) and myocardial ischaemia (1%). Some of these cases were fatal. Other serious and potentially life-threatening adverse events with carfilzomib include pulmonary and hepatic toxicities, pulmonary hypertension, dyspnoea, hypertension, acute renal failure, tumour lysis syndrome, infusion reactions, thrombocytopenia, posterior reversible encephalopathy syndrome and thrombotic microangiopathy. Patients need to be closely monitored during treatment and the dose of

Table **Efficacy of carfilzomib in multiple myeloma**

Study	Treatment (no. of patients)	Median progression-free survival	Overall response rate*
ASPIRE[1]	Carfilzomib with lenalidomide + dexamethasone (396 patients)	26.3 months	87.1% (31.8% had a complete response or better)
	Lenalidomide + dexamethasone (396 patients)	17.6 months	66.7% (9.3% had a complete response or better)
ENDEAVOR[2]	Carfilzomib + dexamethasone (464 patients)	18.7 months	76.9% (12.5% had a complete response or better)
	Bortezomib + dexamethasone (465 patients)	9.4 months	62.6% (6.2% had a complete response or better)

* Overall response rate was defined as the proportion of patients achieving a partial response or better.

carfilzomib may need to be reduced or stopped until symptoms have resolved. Checking hydration, fluid requirements and electrolytes is important.

This drug is not recommended during pregnancy and contraception should be used during treatment. There are no data in humans but carfilzomib caused embryo-fetal toxicity in pregnant rabbits. It is not known if the drug is excreted in breast milk.

Carfilzomib is administered in 28-day cycles. An intravenous infusion is given on two consecutive days each week for three weeks followed by a 12-day rest period. After administration, carfilzomib is rapidly metabolised by peptidase cleavage and epoxide hydrolysis and the inactive metabolites are excreted in the urine. On the basis of preliminary data, interactions with other medicines are not expected.

Consider giving patients antiviral prophylaxis to prevent herpes zoster infection. Thromboprophylaxis is recommended in patients also receiving lenalidomide and dexamethasone depending on their risk.

More than 75% of pre-treated patients appeared to respond to carfilzomib when given as combination therapy. However, it is not yet known if it will extend survival. Toxicity may limit treatment and fatal reactions can occasionally occur so monitoring is paramount.

TT manufacturer provided additional useful information

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At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 False

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