Australian Prescriber

AN INDEPENDENT REVIEW

nps.org.au/australianprescriber

February 2017
Volume 40 Number 1

NPS MEDICINEWISE

CONTENTS

EDITORIAL

Antimicrobial use and resistance in Australia

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Keywords
antibiotics, antibiotic resistance, bacterial infections

Aust Prescr 2017;40:2–3
http://dx.doi.org/10.18773/austprescr.2017.007

Managing the emergence and increasing resistance to antimicrobials in hospitals and the community has become an urgent national and international problem.[1] As part of a plan to tackle this, Australia is developing a coordinated national program to monitor antimicrobial use and resistance.[2]

In 2013, the Department of Health and the Department of Agriculture began to develop a 'one health' approach to resistance management, and released the National Antimicrobial Resistance Strategy in June 2015.[3] One of the seven objectives was surveillance. The Australian Commission on Safety and Quality in Health Care was assigned the task of establishing this surveillance program, and set up the Antimicrobial Use and Resistance in Australia (AURA) project. The first national AURA report was released in June 2016.[4]

The Commission used a structured approach to ensure that all relevant data in human health were included. Both passive and targeted surveillance strategies were used to capture data on antimicrobial use and resistance. The Commission identified existing programs that were national or could become national:

- the National Antimicrobial Usage Surveillance Program (NAUSP) was collecting and publishing data on hospital antimicrobial use
- the Pharmaceutical Benefits Scheme (PBS) was collecting data on antimicrobial prescriptions in the community
- the National Antimicrobial Prescribing Survey was collecting data on appropriate use and compliance with guidelines in hospitals
- the NPS MedicineInsight program was collecting data on appropriate use in general practice
- the Australian Group on Antimicrobial Use and Resistance was collecting resistance and some outcome data on selected pathogens causing bacteraemia originating in hospitals and in the community
- Queensland Health had a data cube capturing all antimicrobial resistance data across Queensland public hospitals (OrgTRx)
- Sullivan Nicolaides Pathology had antibiogram data from community and aged-care settings across Queensland and northern New South Wales
- the National Neisseria Network was collecting and reporting on resistance data for *Neisseria gonorrhoeae* and *N. meningitidis*
- the National Notifiable Diseases Surveillance System was collecting data on *Mycobacterium tuberculosis* from all mycobacterial reference laboratories.

The Commission reviewed these programs for suitability and national coverage, and enhanced and expanded them where necessary. This was largely achieved by the time the first national report was prepared. The report was prepared along similar lines to those generated by the benchmark countries in Scandinavia and the Netherlands, but also included data on appropriate antimicrobial use. The benchmark countries do not currently survey this.

The first AURA report focuses primarily on data from 2014, as this is the first year where complete data were available from all programs.[4] Historical data were included when they were reliable and useful for interpretation. Where possible, comparisons with other countries were made on overall antibiotic use and on key pathogens.

The main findings in antimicrobial resistance data were:

- Rates of resistance in *Escherichia coli* in 2014 were 40–52% for ampicillin or amoxicillin, 20–30% for trimethoprim (slightly lower for the trimethoprim/sulfamethoxazole combination), 18–21% for amoxicillin/clavulanate, 4–16% for norfloxacin, and 0–10% for ceftriaxone. Results depended on the clinical setting – public hospitals and residential aged-care facilities were associated with the higher resistance rates. About 13% of strains were resistant to more than three drug classes.
- Rates of methicillin-resistant *Staphylococcus aureus* (MRSA) were 11–28% depending on the clinical setting. The highest rates were observed in public hospitals and residential aged care. Community-associated clones accounted for more invasive infections (such as bloodstream infections) than hospital clones. The incidence of invasive MRSA infections and the proportions of community-associated MRSA clones varied significantly between states and territories.

- The prevalence of reduced susceptibility to ceftriaxone and azithromycin in *N. gonorrhoeae* was very low but is increasing slowly.
- *N. meningitidis* remains susceptible to the two main antimicrobials used for primary treatment (benzylpenicillin and ceftriaxone).
- Resistance to ampicillin, ceftriaxone and ciprofloxacin in *Salmonella* species is low except for human-associated 'typhoidal' serotypes.
- The proportion of multidrug resistant *M. tuberculosis* is low (<3%).
- In terms of healthcare-associated pathogens, rates of resistance to key antimicrobials are quite low in *Acinetobacter* species and *Pseudomonas aeruginosa*.

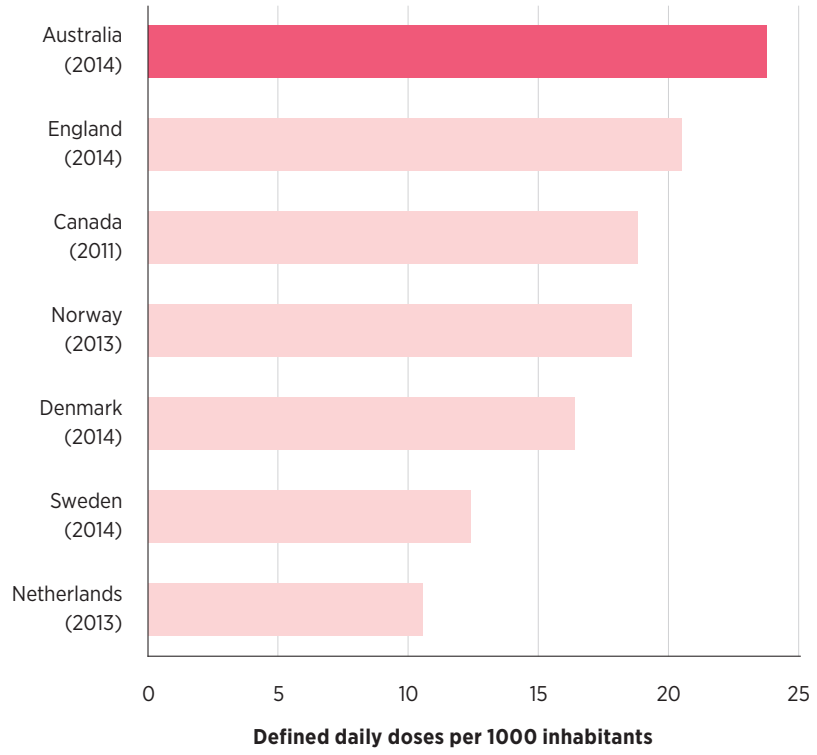
The main findings on antimicrobial use were:

- Antimicrobial use in Australian hospitals is moderately high (936 defined daily doses per 1000 occupied bed days) when compared to similar countries that have data. However, there is evidence of a downward trend since 2010.
- In the national hospital survey in 2014, 38% of patients were receiving antimicrobials on any given day. Of these, 77% were considered appropriate and 76% were compliant with national or local guidelines.
- In the 2015 pilot survey of residential aged-care facilities, 11% of patients were receiving antimicrobials but only 4.5% had a suspected or confirmed infection.
- Antimicrobial use in the community was very high in 2014 when compared to similar countries (see Fig.).
- Thirty million prescriptions for systemic and topical antimicrobials were dispensed on the PBS and 1164 prescriptions for systemic antimicrobials per 1000 inhabitants. The proportion of narrow-spectrum antimicrobials prescribed was low (approximately 5%).
- In the NPS MedicineInsight program, excessive prescribing was identified for acute undifferentiated upper respiratory infection, acute bronchitis, tonsillitis, sinusitis and otitis media.

The AURA report collates valuable national information for the first time on antimicrobial use and resistance. Major areas for improvement in antimicrobial use have been identified in hospitals, residential aged care and especially in the community. The report provides baseline and some trend data on the resistances that are triggered by this use. The AURA program will continue to develop and refine its approach to national surveillance, and become a major part of the national strategy to contain antimicrobial resistance. It will provide the necessary data for monitoring the effects of interventions to reduce inappropriate use through stewardship and regulation, as described in the National Antimicrobial Resistance Strategy.[3]

Conflict of interest: none declared

Fig. **Community antimicrobial use in Australia and other similar countries**



Source: Reference 4

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LETTERS

Letters to the Editor

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

Australian Prescriber distribution

Aust Prescr 2017;40:4
http://dx.doi.org/10.18773/austprescr.2017.008

I am quite disappointed that print publication has ceased as I really enjoy reading *Australian Prescriber* and find it to be a very useful resource. I live in Bamaga, Northern Peninsula Area, which is at the most northern point of Queensland. As you can imagine it is very remote and isolated where I live.

We have limited access to the internet and when we do have access it is very slow and most pages will not load up. I tried to get onto the nps.org.au/australianprescriber site and waited for 50 minutes and it still did not upload so I was not even able to subscribe for the digital edition. I am sure I am not the only remote clinician that is having this problem.

I would be happy to pay a price to receive the printed form of *Australian Prescriber* as I am simply unable to access the electronic version. I feel it is unreasonable for us remote clinicians to miss out on this valuable updated information to assist us to provide evidenced-based practice and to participate in continual learning opportunities.

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Editorial note

Australian Prescriber is now embedded in the new NPS MedicineWise website, which is being improved. The Editorial Executive Committee is interested to know if other clinicians would consider paying for a paper copy of *Australian Prescriber*.

ARTICLE

Extemporaneously compounded medicines

SUMMARY

Extemporaneously compounded medicines may be useful when a required dose or dose form is unavailable commercially, or for individualised dosing.

There are numerous established compounding formulae available, and new formulae may be developed with the help of formulation guidelines and professional advice.

Unlike registered medicines, compounded preparations have not generally been assessed for safety and efficacy. Their use is off label and is based on extrapolation from the component ingredients.

Short-term expiry dates are provided for compounded products unless their stability has been assessed.

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Keywords
dispensing medication, drug compounding, drug control, off-label prescribing

Aust Prescr 2017;40:5–8
http://dx.doi.org/10.18773/austprescr.2017.001

Corrected 10 May 2017
This is the corrected version of the article.
Correction notice available at: http://dx.doi.org/10.18773/austprescr.2017.042

Introduction

Extemporaneous compounding is the preparation of a therapeutic product for an individual patient in response to an identified need.[1] It is a practical way to have medicines supplied when there is no other option. For example, compounding may be useful for patients with dysphagia who are unable to swallow solid medications whole, when an appropriate dose or dosage form is not commercially available, when patients require an individualised dose, or when medicines must be delivered via nasogastric or gastrostomy tubes.[2]

Active pharmaceutical ingredients can be incorporated into a wide array of products including creams, eye drops, nasal sprays, oral dosage forms or intravenous infusions. In Australia, products may be classified into simple or complex compounding (Table 1). Simple compounding can be performed by any pharmacist and is a core competency of pharmacy training. Complex compounding requires additional training and evidence, as described by the Pharmacy Board of Australia's guidelines on compounding.[1]

Regulation

The final medicine produced by compounding is regulated according to the component's schedule in the Poisons Standard (the SUSMP).[3] For example a topical progesterone (S4) cream requires a

Table 1 **Classification of simple versus complex compounding**

Compounding type	Explanation	Examples
Simple	All pharmacists have training during their undergraduate degree to prepare these products. Involves well-established preparations published in reputable literature, e.g. the Australian Pharmaceutical Formulary and Handbook, or formulae for which some data are available regarding quality, stability, safety, efficacy and rational design.	Topical creams, ointments, lotions, gels, e.g. steroids, hormones, coal tar, cholestyramine Oral liquids (solutions, suspensions, emulsions, mixtures, elixirs), tinctures, e.g. omeprazole suspension Capsules, tablets, powders, e.g. boric acid capsules Suppositories, pessaries, e.g. paracetamol, clotrimazole
Complex	Pharmacists require further postgraduate training in association with self-assessment of relevant competencies and documentation of the specific competencies in a continuing professional development plan. Specialised facilities (sterile room with positive pressure) and equipment (laminar flow isolator, dry heat sterilisation oven) are also required.	Parenterals, e.g. morphine, clonidine Ingredients with a safety hazard, e.g. cytotoxics, hormones Single unit micro-dose (<25 mg of drug or no more than 25% w/v of a dosage form), e.g. naltrexone Modified-release dosage forms, e.g. levothyroxine (T4), progesterone capsules Ophthalmic preparations, e.g. phenylephrine, tropicamide, ciprofloxacin

Source: Reference 1

prescription whereas dithranol (S3) ointment can be supplied without instructions from a medical practitioner. In contrast, a pharmacist must have been instructed by a veterinary surgeon to compound medicines for an animal irrespective of the scheduling of the active ingredient. All components of a compounded product, that is the active ingredient and the excipients, are subject to quality standards set out in the *Therapeutic Goods Act 1989*, and are sourced from compounding supply companies that undertake rigorous quality-assurance testing.

The Therapeutic Goods Administration (TGA) specifies that all medicinal products must meet the PIC/S* Guide to Good Manufacturing Practice for Medicinal Products, which is an international standard.[4] However, it is important to be aware that the final medicine produced by extemporaneous compounding is exempt from assessment by the TGA.

Commercially available medicines must be listed or registered in the Australian Register for Therapeutic Goods (ARTG) (see Box), unless exempt by the Therapeutic Goods Regulations. They are manufactured by TGA-licensed manufacturers and undergo extensive testing to ensure an accurate dose of active drug will be delivered in a reasonably reproducible manner. Commercially available medicines are also tested for stability so an expiry date can be provided. Extemporaneously compounded medicines are not listed or registered, and no assessment of the final medicinal product in terms of quality, stability or efficacy is required.

Where are compounded products made?

Extemporaneous compounding takes place in community and hospital pharmacies. There are usually specialist compounding pharmacies in major towns and cities, but any pharmacy may undertake compounding as long as they have appropriate facilities according to state-based legislation (e.g. allocated clean bench, specific compounding equipment).

Complex compounding is performed in a pressurised clean room using a laminar flow cabinet, cytotoxic drug safety cabinet or an isolator.[1] Many public and private hospitals maintain large aseptic compounding facilities to provide individualised dosing or commercially unavailable formulations.

* Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

Box Commercially available and compounded medicines in Australia

Commercially available medicines

These products must be listed (AUST L) or registered (AUST R) on the ARTG. Listed medicines are evaluated for quality and safety by the TGA and include vitamins and mineral supplements and herbal medicines. Registered medicines are evaluated for quality, safety and efficacy by the TGA and include all prescription medicines, most over-the-counter medicines (e.g. analgesics) and some complementary medicines (e.g. high-dose calcium supplements).

Extemporaneously compounded medicines

These products are prepared according to PIC/S Guide to Good Manufacturing Practice for Medicinal Products. However, they are not listed or registered on the ARTG and assessment of the quality, stability and efficacy of the final product is not required.

ARTG Australian Register of Therapeutic Goods
TGA Therapeutic Goods Administration
PIC/S Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

How is compounding performed?

The active ingredient may be derived from commercially available medications or the pure chemical. Sometimes compounding is as simple as mixing a crushed tablet or the contents of a capsule in water to form a solution or suspension. However, this may not be suitable and depends on the solubility of the active ingredient. For example, insoluble tablet excipients can lead to blockages in enteral feeding tubes.[5] In the majority of compounded products, additional non-active components (excipients) are included to ensure the active ingredient dissolves or remains suspended, or to adjust palatability or viscosity.[6]

A range of proprietary bases and excipient mixes are available commercially through compounding suppliers to create preparations such as capsules, rapidly dispersing tablets, creams, gels, ointments, oral liquids, lozenges, troches and suppositories. This can simplify the preparation protocol and provide some background research, development and quality control for the base. All pharmacies are required to document the compounding protocol used and maintain records of all compounded products dispensed.

Compounding formulae

It is preferable to use standardised formulae, especially when some stability information is available. Formulae and associated preparation

protocols are available for some of the more commonly compounded products, for example the current edition of the Australian Pharmaceutical Formulary and Handbook[7] describes approximately 130 formulae. Over 1000 other formulae may be found in older editions.[8] Formulae may also be found through specialist journals and websites. Pharmacies that regularly compound, particularly hospital and compounding pharmacies, often have their own compendium of formulae for products that they dispense on a regular basis. The formulae are documented in the form of a batch sheet that precisely describes the compounding method and allows for documentation of the ingredients used.

Advice is available from experienced pharmacists that work for the companies that supply the raw materials in Australia, such as the Professional Compounding Centers of America (membership required), Medisca and Bella Corporation (no membership required). They can help to develop formulae that will theoretically optimise drug delivery and minimise instability.

Stability of products

In most instances, the actual stability of the drug in the final compounded medicine is not known. Larger compounding companies or hospitals may undertake or outsource stability testing for a particular product, and will reference published stability information when preparing their batch sheets. Information regarding the chemical stability of the active ingredients can inform product design and expiry date. Active ingredients may degrade when exposed to oxygen and water, with reactions being initiated and accelerated by light, heat or certain trace metals (see Table 2).[9,10] For example, active ingredients containing an ester functional group, such as aspirin and penicillins, are susceptible to breakdown by hydrolysis, while those containing aldehyde or hydroxyl groups, such as testosterone and dopamine, undergo oxidative decomposition. A 10°C increase in temperature can result in a 2–5-fold faster rate of degradation.

It is essential that the active ingredient does not interact with any excipients originating from the dosage form being crushed for reformulation (e.g. tablet lubricants and fillers), or from additives in the new formulation (antioxidants, preservatives, suspending agents, colourants, emulsifiers). Interactions with other ingredients can result in physical instability of the product, such as precipitation of the active drug or phase separation ('cracking') of a cream, affecting drug solubility, absorption and bioavailability.

To minimise the risk of a compounded medicine degrading, short-term expiry dates are used (e.g. 28 days for oral and topical products, or 24 hours for parenteral formulations), unless stability studies have been conducted and indicate otherwise.

Sterility of products

Microorganisms may grow if the water content is high enough so exposure to an aqueous environment can cause medicines to 'spoil'. Contamination can cause instability of the formulation or drug degradation, or both.

Microorganisms could potentially be introduced during reformulation of non-sterile products. For example, if *Candida albicans* is inadvertently introduced into freshly prepared multi-dose citric acid solutions that are to be used orally for cough reflex testing, immunocompromised individuals could become infected.[11] Including a preservative is the most common approach for non-sterile water-based compounded products, especially when storage for more than a few days is required. Many factors affect the choice of preservative, such as dosage form and pH of the product. Refrigerated storage can help delay deterioration.

Table 2 **Common degradation pathways of active drugs in compounded products**

Pathway	Factors determining degradation rate	Susceptible functional groups	Examples[9,10]
Oxidation (O_2 dependent)	Concentration of drug, temperature, catalysts, solvents, light and excipients	Aldehydes, alcohols, phenols, alkaloids, unsaturated alkyl chains, carboxylic acids	Paracetamol, progesterone, testosterone, quinine, oils (unsaturated fats) such as soybean and corn oil, essential fats, atorvastatin, atenolol
Hydrolysis (H_2O dependent)		Esters, amides, lactones, ethers, lactams, imines, acetals, anhydrates, sulfonamides	Aspirin, vigabatrin, norfloxacin, omeprazole, simvastatin (statins), baclofen, diphenoxylate, methylphenidate, lignocaine, sildenafil, penicillins, cephalosporins, diazepam, digoxin, heparin, captopril, hydrocortisone

Note: drug molecules with more than one functional group can be more easily degraded. In fact, many drugs contain more than one functional group, being susceptible to both oxidation and hydrolysis, e.g. atenolol (contains amide and alcohol groups).

Parenteral products are compounded by appropriately trained staff using aseptic techniques. Multiple-use products will contain a suitable preservative, while single-use syringes or infusions rely on good aseptic practice. Regular monitoring of the environment, equipment and procedures is essential to ensure quality and sterility is maintained. The consequences of failure can be catastrophic, for example methylprednisolone injections from a single compounding pharmacy in the USA resulted in 137 cases of *Aspergillus fumigatus* meningitis and 12 deaths.[12]

Conclusion

Medicines are commonly prepared by extemporaneous compounding in Australia and around the world when commercial preparations are unavailable or individualised dosing is required. They do not have to be listed or registered on the ARTG because they are prepared for an individual patient. The quality of the components are assured by purchase from reputable suppliers, and quantities used and the formulation method are thoroughly documented within the pharmacy. The preparation of compounded medicines is subject to strict international standards, but they are generally dispensed without any testing for content, consistency, stability and sterility.

There is published information regarding chemical degradation of the active drug and for many compounding formulae. However, usually there are no data to inform the pharmacist or patient about a specific product's quality or stability. Products are typically freshly prepared with a relatively short-term expiry date based on guidelines in the Australian Pharmaceutical Formulary and Handbook [7] to limit the risk of degradation or contamination by microorganisms. <

Conflict of interest: none declared

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Australian Prescriber
VOLUME 40 : NUMBER 1 : FEBRUARY 2017

ARTICLE

Phosphate binders in patients with chronic kidney disease

SUMMARY

Hyperphosphataemia in patients with chronic kidney disease, particularly those on dialysis, can be ameliorated by oral phosphate binders in conjunction with dietary phosphate restriction.

Although phosphate binders reduce serum phosphate in these patients, it remains uncertain whether they improve clinical outcomes.

Calcium-based binders are frequently used, but their popularity is waning due to emerging evidence of accelerated vascular calcification.

The use of aluminium-based binders has been limited by a perceived risk of aluminium accumulation.

The non-calcium-based phosphate binders – sevelamer hydrochloride, lanthanum carbonate and sucroferric oxyhydroxide – have become available and subsidised by the Pharmaceutical Benefits Scheme for patients on dialysis.

The pill burden and adverse effects (particularly gastrointestinal intolerance) associated with phosphate binders often contribute to poor medication adherence.

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Keywords
chronic kidney disease, drug compliance, drug costs, hyperphosphataemia, phosphate binders, pill burden

Aust Prescr 2017;40:9–14
http://dx.doi.org/10.18773/austprescr.2017.002

Introduction

Hyperphosphataemia is an independent predictor of cardiovascular disease and mortality in patients with advanced chronic kidney disease (stage 4 and 5) and is due to impaired phosphate excretion by the kidney.[1-3] It is typically managed with oral phosphate binders in conjunction with dietary phosphate restriction. These drugs aim to lower serum phosphate by reducing intestinal absorption of dietary phosphate. Hyperphosphataemia is normally asymptomatic. However, phosphate binders may provide symptomatic relief from pruritus and red irritated eyes, which are more commonly reported in patients with serum phosphate elevations greater than 1.8 mmol/L.[4,5]

Phosphate binders are a commonly prescribed class of drug for patients on dialysis. In Australia, the annual expense for phosphate binders has increased significantly since sevelamer hydrochloride and lanthanum carbonate were included on the Pharmaceutical Benefits Scheme (PBS), with the mean pill cost increasing from $12.85 to $59.85 per patient per week.[6] There is a lack of trial evidence for both benefit in patients and cost-effectiveness of phosphate lowering.[7] Phosphate binders may also account for up to 50% of the daily pill burden in patients with chronic kidney disease.[8] Together with frequent adverse drug effects (particularly gastrointestinal intolerance), this contributes to poor medication adherence.[9]

Phosphate binders

There are three main types of phosphate binders available – calcium-containing binders and aluminium-containing binders, which have been around for many years and are cheap, and the new non-calcium-based binders (sevelamer, lanthanum and sucroferric oxyhydroxide) which are considerably more expensive (see Table).[1-3]

Calcium carbonate is the most common form of phosphate binder prescribed, particularly in non-dialysis chronic kidney disease. It is typically given to patients with advanced chronic kidney disease, including those receiving dialysis. As with all phosphate binders, calcium-based binders are most effective when taken with meals (which also limits calcium absorption).[10] They should be prescribed in conjunction with moderate dietary phosphate restriction, ideally supervised by an accredited practising dietitian. Phosphate-rich foods with a high phosphate to protein ratio (processed foods, fast foods and cola drinks) are best avoided, while foods with a high biologic value (e.g. meats and eggs) should be retained to maintain nutritional status.[11,12]

Aluminium-based binders are a second-line drug in non-dialysis chronic kidney disease. The other newer non-calcium-based binders – sevelamer, lanthanum and sucroferric oxyhydroxide – are only available under the PBS for dialysis patients.

Table **Characteristics of oral phosphate binders available in Australia**

Phosphate binders	Mechanism of action	Form, strength	Initial dose	Maximum recommended dose	Cost per tablet	Advantages	Disadvantages
Aluminium hydroxide	Forms insoluble phosphate complexes in the gut	600 mg tablets	1 tablet 3 times a day with meals	2 tablets 3 times a day with meals	20 cents	Inexpensive, calcium-free, binds phosphate at wide range of pH	No safe dose established, significant adverse effects (e.g. potential central nervous system toxicity, microcytic anaemia, osteomalacia, gastrointestinal upset), requires regular monitoring of serum aluminium
Calcium carbonate	Forms insoluble phosphate complexes in the gut	Chewable tablets, 500 mg, 600 mg elemental calcium	1 tablet 3 times a day with meals	1 tablet 3 times a day with meals	17 cents	Moderately effective, relatively inexpensive	Hypercalcaemia, large doses required to be effective, possible vascular calcification, unpalatable
Sevelamer hydrochloride	An anion exchange resin	800 mg tablets	1–3 tablets a day with meals	0.3 g/kg/day	$1.72	Calcium-free, lipid-lowering effect	Expensive, high pill burden, gastrointestinal adverse effects (bloating)
Lanthanum carbonate	Forms insoluble phosphate complexes in the gut	500 mg, 750 mg, 1000 mg chewable tablets	500–750 mg 3 times a day with meals	1000 mg 3 times a day with meals	500 mg $2.91, 750 mg $4.39, 1000 mg $4.94	Low pill burden, high efficacy, works in wide range of pH, no negative changes on bone histology	Expensive, gastrointestinal adverse effects, uncertain long-term effects
Sucroferric oxyhydroxide	A ligand exchange iron-based compound	500 mg chewable tablets	1 tablet 3 times a day with meals	6 tablets per day	$4.19	Low pill burden, works in wide range of pH, minimal systemic absorption	Expensive, gastrointestinal adverse effects (stool discoloration)

For all binders except lanthanum and sucroferric oxyhydroxide, the starting dose is typically 1–2 tablets three times daily with each meal, depending on potency. Between-meal snacks are often covered with half a tablet. For calcium-based binders and sevelamer, the dose can be increased to a maximum of six or more tablets daily. Other medicines should be given separately as phosphate binders can interfere with the absorption of drugs such as oral iron[13] and ciprofloxacin.[14]

Calcium-containing phosphate binders

Calcium binders have historically been an appealing first choice, because they also address the hypocalcaemia that is often seen with hyperphosphataemia in patients with chronic kidney disease. However, hypercalcaemia and accelerated vascular calcification are the main concerns with calcium-containing phosphate binders, particularly when they are combined with vitamin D therapy.[5,15-18]

The Kidney Disease Outcomes Quality Initiative Guidelines suggest that doses should not exceed 1500 mg/day of elemental calcium,[19] based on evidence that this produces a positive calcium balance (excess body stores of calcium leading to soft-tissue and vessel calcification) in chronic kidney disease.[20] However, there is little evidence of patient outcomes to support this recommendation. Another common adverse effect of these drugs is gastrointestinal upset, particularly constipation. The other main advantage of calcium-based binders is that they are inexpensive.

Aluminium-containing phosphate binders

Aluminium hydroxide has an excellent phosphate-binding capacity and has been used for over three decades. A number of (principally US-based) guidelines advise against long-term use of aluminium-based binders because of concerns about aluminium intoxication (dementia, osteomalacia, anaemia).[21] This is despite little evidence of toxicity with these

drugs in an era of ultrapure dialysis water quality.[22] Some European countries as well as Australia still use aluminium for this purpose but regular testing of dialysis water is mandatory if aluminium is to be used orally. Also, oral citrate must be avoided in patients taking aluminium binders as this has been shown to lead to enhanced absorption and cases of neurological toxicity.[23] There are a limited number of small randomised trials examining the efficacy and safety of aluminium as a binder. However, they were inadequately powered for examining patient-level outcomes.[24-29]

Sevelamer hydrochloride

Sevelamer is the most commonly prescribed non-calcium-based phosphate binder, but has a lower phosphate-binding capacity than other phosphate binders. Its off-target effects include lowering serum low-density lipoprotein cholesterol and increasing the concentrations of fetuin-A (calcification inhibitor).[30] However, these effects have not been shown to improve cardiovascular outcomes for dialysis patients in prospective trials.

The primary disadvantages of this drug are its high price and high pill burden. It may also reduce the bioavailability of fat-soluble vitamins. Its main adverse effects are gastrointestinal intolerance and metabolic acidosis.[31]

Lanthanum carbonate

Lanthanum is a trivalent metal phosphate binder which has a similar affinity for phosphate as aluminium-based drugs.[32] It is roughly twice as potent as calcium and sevelamer. Lanthanum powder is more effective than chewable tablets[33,34] and reduces the pill burden.[35] It is also the only oral phosphate binder to come in three different tablet strengths, meaning the maximum number of tablets per day is always three. Despite poor intestinal absorption, lanthanum may deposit in tissues, particularly liver and bone.[36] However, in studies with extended follow-up there is no evidence of clinical hepatotoxicity[37] and bone toxicity.[38,39] Like other phosphate binders, lanthanum may cause gastrointestinal intolerance, particularly nausea. Similarly to sevelamer, this drug is expensive.

Sucroferric oxyhydroxide

Sucroferric oxyhydroxide is now registered in Australia as an iron-based phosphate binder for patients with chronic kidney disease on dialysis. Phosphate binding occurs across a wide range of stomach pH, with a peak at pH 2.5.[40] Common adverse effects include diarrhoea and change in stool colour. There was no evidence of iron accumulation in a phase III extension study.[41,42] The binder has a similar pill burden to lanthanum carbonate, as it is given as one pill with each meal and is easily chewable, which may improve patient adherence.[43] The cost of sucroferric oxyhydroxide is similar to lanthanum and sevelamer.

Other phosphate binders

A number of other drugs have been used as phosphate binders, including sevelamer carbonate,[44] calcium acetate,[45] magnesium carbonate,[46] ferric citrate,[47] colestilan,[48] bixalomer[49] and nicotinic acid[50] but are not registered in Australia for this purpose.

How effective are phosphate binders in chronic kidney disease?

Despite evidence that phosphate binders reduce serum phosphate, a recent Cochrane review involving 7631 participants from 60 studies found no convincing evidence for improvements in all-cause or cardiovascular mortality, vascular calcification or fracture risk.[51]

Calcium-based binders were associated with significantly lower serum phosphate (mean difference 0.07 mmol/L) when compared with sevelamer. However, sevelamer was associated with a lower risk of hypercalcaemia (risk ratio 0.45, 95% CI* 0.35–0.59) and a higher risk of adverse gastrointestinal events (risk ratio 1.58, 95% CI 1.11–1.25). There was no difference in all-cause mortality between calcium-based binders and sevelamer.[51]

A meta-analysis of 11 randomised, controlled trials found that patients treated with non-calcium-based binders had a 22% decreased risk of all-cause mortality (risk ratio 0.78, 95% CI 0.61–0.98) compared with patients treated with calcium-based binders.[52] However, the results were limited by moderate trial heterogeneity. No significant benefit of non-calcium-based binders was evident in large trials, or after correcting for publication bias or removing a trial with a high risk of bias.[53-55]

A recent meta-analysis of phosphate binders reported that no phosphate binder reduced mortality compared to placebo in adults with chronic kidney disease.[56] More importantly, sevelamer resulted in lower mortality than calcium-based drugs, while the comparative effects of lanthanum, iron-based drugs and colestilan were less certain.[56]

Phosphate binders therefore effectively reduce serum phosphate in patients with chronic kidney disease, but it is uncertain whether they improve clinical outcomes. There may be a mortality difference between calcium-based and non-calcium-based binders, but it is not

* confidence interval

clear if this reflects a harmful effect of calcium-based binders, a beneficial effect of non-calcium-based binders or both.

This raises the economic argument of cost-effectiveness. The older binders such as calcium carbonate and aluminium hydroxide are cheaper (a few cents per tablet) than the newer binders sevelamer, lanthanum and sucroferric oxyhydroxide (see Table). This makes use of the newer binders potentially harder to justify.[54,55]

Guidelines

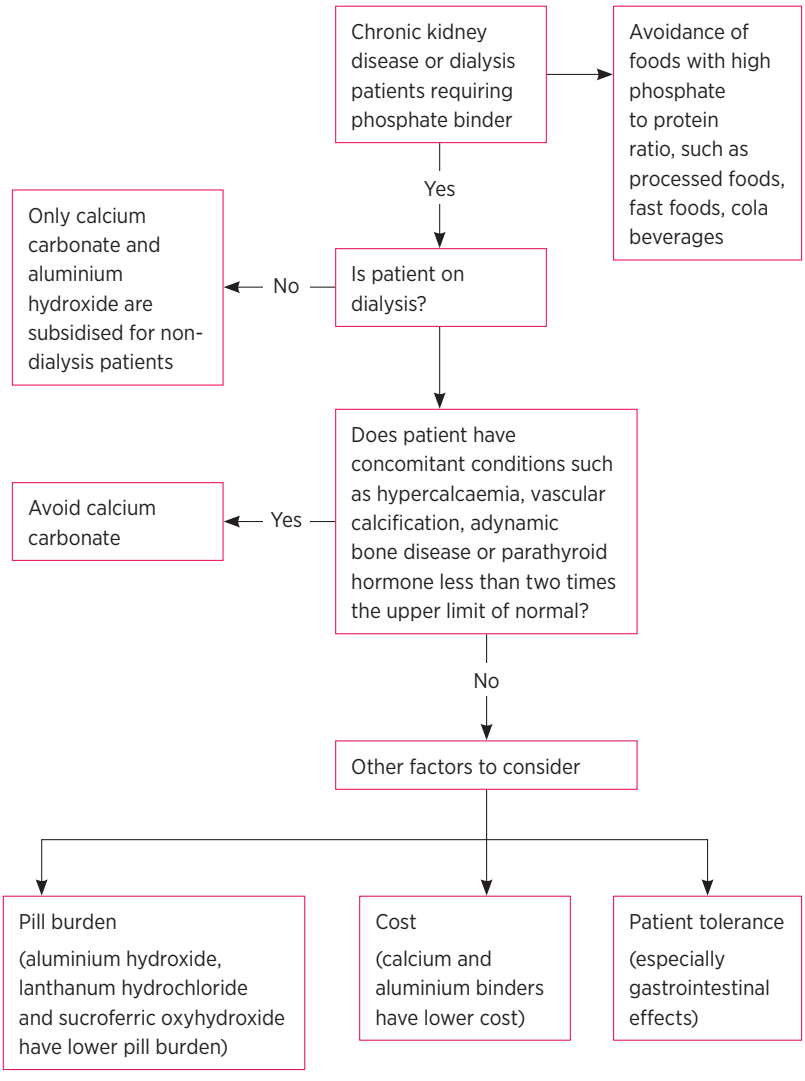
Based on poor quality and conflicting evidence, guidelines make weak suggestions that oral phosphate binders should be used for hyperphosphataemia-complicating chronic kidney disease to maintain serum phosphate in the normal range.[22] They also suggest that calcium-based binders should be dose restricted (or avoided) in the following circumstances:

- the presence of hypercalcaemia
- arterial calcification
- adynamic bone disease (a low bone turnover condition) or serum parathyroid hormone concentrations that are less than two times the upper limit of the laboratory reference range.†

Long-term use of aluminium-based binders is advised against because of the potential risk of toxicity.

The Kidney Health Australia guidelines – Caring for Australasians with Renal Impairment (KHA-CARI) – recommend that phosphate binders are effective in reducing serum phosphate in advanced kidney disease.[57] Calcium salt-based binders are recommended as first-line drugs but their use should be minimised when serum calcium is above the target range (2.4 mmol/L) or serum parathyroid hormone is below the upper limit of the reference range.[57]

Fig. **Prescribing phosphate binders for hyperphosphataemia in patients with chronic kidney disease**



Conclusion

Oral phosphate binders are widely used for hyperphosphataemia in patients with advanced chronic kidney disease, although it remains uncertain whether they improve patient outcomes such as renal bone disease, cardiovascular events and mortality.

Calcium carbonate is the most commonly used phosphate binder, but clinicians are increasingly prescribing the more expensive, non-calcium-based phosphate binders, particularly sevelamer.[6] This is primarily because emerging evidence suggests calcium-based binders may accelerate vascular calcification and cardiovascular mortality.

If a phosphate binder is prescribed, choice will be influenced by whether or not the patient is on dialysis because non-calcium binders (lanthanum carbonate, sevelamer hydrochloride and sucroferric oxyhydroxide) are not available on the PBS for non-dialysis patients. Cost, concomitant conditions, pill burden and patient tolerance should also be considered (see Fig.). Prescription should be accompanied by dietary advice, patient education and regular assessment of adherence.

Conflict of interest: none declared

† The desired parathyroid hormone concentration in chronic kidney disease is more than two times the upper limit of normal. If it is less than this, the patient may be at risk of adynamic bone disease.

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ARTICLE

Drugs for chronic obstructive pulmonary disease

SUMMARY

Chronic obstructive pulmonary disease is a complex disease, with both pulmonary and systemic manifestations. There is an increased risk of serious comorbidity and mortality.

Although chronic obstructive pulmonary disease is most often progressive, both pharmacological and non-pharmacological interventions significantly ameliorate the severity and impact of symptoms, and reduce the frequency of exacerbations.

Stopping smoking and pulmonary rehabilitation are key interventions.

Mild symptoms are managed with short-acting inhaled bronchodilators. One or two long-acting bronchodilators are added if symptoms persist. The role of inhaled corticosteroids is being questioned as they may not benefit all patients.

Optimal therapy includes reviewing patients' inhaler use, and ensuring they have a self-management plan that enables them to promptly start treatment of infection and exacerbations. In future, treatment is likely to combine a multidimensional management approach with tailored treatment and clinical phenotyping.

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Keywords
antimuscarinics, beta agonists, COPD (chronic obstructive pulmonary disease), corticosteroids

Aust Prescr 2017;40:15–9
http://dx.doi.org/10.18773/austprescr.2017.003

Introduction

The optimal management of chronic obstructive pulmonary disease (COPD) requires a multifaceted approach which incorporates non-drug as well as drug-management strategies. It is a complex disease, with both pulmonary and systemic manifestations, and an increased risk of serious comorbidity and mortality. For most patients, it has a major impact on lifestyle and quality of life. Although it has not been studied systematically, early treatment is likely to help sustain lung function.

Assessment

There is a wide variability in symptom severity and this correlates relatively poorly with lung function as measured by the forced expiratory volume in one second (FEV_1). Generally symptoms worsen over time.[1,2] Patients' symptoms should be assessed in their own right to guide management, rather than relying on the FEV_1 which is an insensitive measure of disease impact.[3] A multidimensional approach to assessment has been advocated by guidelines in recent years. This gives objective targets for assessing symptoms and their response to treatment. The Australian COPD-X guidelines[4] recommend a thorough assessment of the patient for the impact of day-to-day symptoms such as breathlessness, cough and sputum, the frequency of exacerbations and their prevention, and the presence of comorbidities.

Patients with COPD often have comorbid conditions beyond those that can be explained by the common pathway of cigarette smoking, including cardiovascular disease, osteoporosis, diabetes, anxiety and depression. They also have comorbidities related to their lung disease such as lower respiratory tract infections. These problems greatly increase the risk of hospitalisation and worsen the quality of life for patients. Hence the identification and management of comorbidities is a crucial aspect of treatment. It is important for these patients to have pneumococcal and influenza immunisation, but reductions in exacerbation rates have only been shown for influenza. In a Cochrane review, influenza vaccination in patients with COPD significantly reduced total exacerbations per vaccinated person compared to those who received placebo.[5]

It is frequently said that patients do not become symptomatic until they have lost approximately 50% of their lung function, but recent evidence from the UK shows that patients present on many occasions to primary care in the 10 years before a formal diagnosis. They often present with episodes of lower respiratory tract infection and persisting productive cough after viral infection.[6] These episodes in smokers and ex-smokers should be regarded as red flags, alerting clinicians to the possibility of COPD.[7]

The diagnosis is confirmed by finding an FEV_1 under 80% of the predicted value and an FEV_1/FVC (forced vital capacity) ratio less than 0.7, in a patient with

a consistent history of smoking or dust and fume exposure. An objective assessment of symptoms based on functional impact should be made, ideally using a validated symptom score such as Medical Research Council (MRC) or COPD assessment test (CAT).[8]

Non-drug therapy

Non-drug interventions are as important as pharmacotherapy in maximising quality of life and minimising the impact of symptoms, risk of exacerbations, and loss of functional capacity.[9] The most important intervention is smoking cessation as it improves the quality of life, reduces the risk of declining lung function and reduces mortality.[10-12]

Pulmonary rehabilitation is a crucial intervention to maximise exercise capacity and quality of life. Although frequently incorporating education, symptom control and self-management strategies, the vital component of pulmonary rehabilitation is a structured exercise program. This is usually implemented by regular participation for eight weeks, under the supervision of a physiotherapist skilled in this area. It is associated with reduced hospital admissions and exacerbations, particularly when it is part of an integrated care approach.[13] Patients with COPD of all severities are suitable for pulmonary rehabilitation and should be actively encouraged to participate.

Maintenance of physical activity is very important for sustaining the benefit and is probably a bigger challenge for many patients than an eight-week course of pulmonary rehabilitation alone. Patients with COPD are markedly inactive compared to age- and sex-matched peers. Nevertheless higher levels of physical activity even in moderate to severe disease are associated with substantially better outcomes in exacerbation risk, hospital admissions and mortality.[14,15]

Drug therapy

Apart from oxygen, no drug has been shown to reduce the increased risk of death in patients with COPD. For this reason drugs are prescribed predominantly to reduce symptoms, improve functional capacity, and prevent and treat exacerbations. Drugs are prescribed in a stepwise fashion.[16] Mild symptoms can be managed with an inhaled short-acting beta agonist (SABA), taken when needed either before exercise or for the relief of exertional breathlessness.[17] Patients who need inhalations several times a week are likely to benefit from adding a long-acting muscarinic antagonist (LAMA) or a long-acting beta agonist (LABA).[18,19]

The choice of second-line drug depends on the patient's response and preference.[18,20,21] While there are few clinically important differences between the LAMAs,[22] there are differences between LABAs which may be more obvious to patients, and are important in affecting their choice.[23] Most importantly, formoterol, indacaterol and vilanterol have a relatively fast onset of action, of 5–10 minutes, while salmeterol has a 30-minute onset. These differences may not be important once patients are taking long-acting bronchodilators regularly. Like salmeterol, formoterol and indacaterol, the newly available LABAs vilanterol and olodaterol have statistically and clinically significant effects on lung function, exercise tolerance, SABA use, dyspnoea, quality of life and exacerbations.[24] LABAs are well tolerated and there are negligible differences between them in relation to adverse effects.[25] Tremor and tachycardia appear to occur less commonly with LABAs than SABAs.

LAMAs include tiotropium, umeclidium, glycopyrronium and aclidinium. There are only small differences between them in efficacy.[26] The duration of action of aclidinium is shorter and therefore it is the only LAMA prescribed in a twice-daily regimen.[27] These drugs have adverse effects which include urinary retention in patients with prostatic enlargement, worsening of glaucoma and atrial arrhythmias. While these effects had a very low prevalence in clinical trials,[28] most studies have excluded patients at risk,[19,27] so it is difficult to know the true prevalence of these adverse effects in the general population of patients with COPD. In a large safety study of tiotropium with cardiac end points, there was no increased mortality or major adverse cardiac effects with tiotropium 5 microgram or 2.5 microgram inhaled daily for a median of one year.[29]

Combination therapy

Guidelines have recommended the addition of inhaled corticosteroids to long-acting bronchodilators when the FEV_1 is less than 50% predicted and the patient has had more than one exacerbation in the previous 12 months.[4,17] In the stepwise management of stable COPD, combination inhaled corticosteroids/LABA therapy is recommended for this group of patients.[16] Many patients will already have been taking a LAMA, so they will be stepping up from a single long-acting bronchodilator to 'triple therapy'. The availability of dual bronchodilators, LABA and a LAMA combined in a single device, has changed this paradigm.

Although there is debate regarding the clinical value of LAMA plus LABA together, compared to either alone, in randomised controlled trials, the combination is generally superior to either drug alone.[18,30-32] Most recently dual bronchodilators have been shown not only to improve lung function, exercise capacity, dyspnoea and reduce the use of short-acting bronchodilators, compared to either LABA or LAMA alone, but also to reduce COPD exacerbations.[33,34]

Since exacerbation reduction is the most important effect of inhaled corticosteroids, the question has arisen whether the addition of inhaled corticosteroids is still the most appropriate step for all patients who have frequent exacerbations. Several studies have tested this using different designs – either withdrawal of inhaled corticosteroids or a comparison of LAMA plus LABA with inhaled corticosteroids plus LABA.[35,36] In one study in which patients took placebo or inhaled corticosteroid during a progressive drop in the dose of inhaled corticosteroids over 12 weeks, the corticosteroid withdrawal was not associated with an increased risk of exacerbations.[35] Patients on placebo lost slightly more lung function than those who received inhaled corticosteroids, but subsequent analysis suggests that this effect plateaus and lung function is not lost at a faster rate in the long term. More studies are required to verify this.

Another problem is the adverse effects of corticosteroids. There is a substantial database and evidence from randomised controlled trials that high-dose inhaled corticosteroids (>500 microgram/day fluticasone propionate or equivalent) are associated with an increased risk of pneumonia in patients with COPD.[37-39]

Effect of eosinophilia

Adding to the controversy regarding the role of inhaled corticosteroids are recent studies suggesting that they are more effective in patients with peripheral blood eosinophilia.[40-42] Although the threshold for this effect has not been verified, a count greater than 300–400/microlitre or 3–4% is the likely cut point. Although systematic reviews suggest that inhaled corticosteroids reduce the risk of exacerbation in COPD by around 25% across all study participants,[43,44] there is significant heterogeneity of effect.[45] Compared to LABA alone, the greatest benefit of inhaled corticosteroids was seen when the peripheral count was more than 400/microlitre.[42] The evidence is therefore accumulating that inhaled corticosteroids are most effective in a particular subgroup of patients and do not confer benefit in others.[46,47] In view of the adverse effects of corticosteroids, it is likely in the future that they will not be prescribed for all patients with COPD and frequent exacerbations.

Patients without eosinophilia may not benefit from inhaled corticosteroids but will still be at risk of adverse effects.[48,49] Further randomised controlled trials are required to verify that corticosteroids should not be prescribed to these patients.

Future developments

Classification of COPD either by the presence or absence of eosinophilia, exacerbation phenotype (infrequent or frequent) or clinical presentation (chronic bronchitis or mucus hypersecretion vs emphysema vs asthma COPD overlap) is now beginning to guide treatment decisions and clinical trials.[50-52] The results of these trials should be of great value in tailoring COPD management, as much of the evidence suggesting that phenotypic classification is helpful comes from retrospective studies. The most convincing data for treating the chronic bronchitis phenotype come from studies of roflumilast (not currently available in Australia), a phosphodiesterase-4 inhibitor which has significant benefit in reducing COPD exacerbations in patients with COPD and mucus hypersecretion.[53] Finally, careful attention to comorbidities, especially co-existing cardiovascular and metabolic disease, is likely to reduce hospital admissions and complications of exacerbations. Future trials are awaited, particularly of cardioselective beta blockers in COPD, as retrospective analyses suggest they are safe but their efficacy in COPD has not yet been tested in randomised controlled trials.

Drug delivery

The marketing of new inhaled drugs for COPD has brought with it a plethora of new devices.[16] It is essential that clinicians familiarise themselves with these and tailor the drug and the device to the patient. Simplifying the regimen is of no value if the new device is not appropriately used. Every new treatment should be considered in the light of the device in which it is delivered and its suitability for each patient. The number of devices per patient should be minimised to help maintain adherence and good inhaler technique. Device use must be demonstrated carefully, and reviewed regularly.

Conclusion

The impression of COPD as a disease with a bleak outlook and minimal benefit from treatments, is no longer appropriate. Major advances in drug therapy and a recognition of the importance of non-drug interventions have dramatically improved the patients' quality of life, symptom severity and exacerbation frequency. Approaching patients with an understanding of the multiple impacts of the disease, assessing and managing comorbidities, and tailoring treatment while assisting them in optimal use of their inhalers is likely to deliver sustained benefits in well-being and disease control. ≺

Christine Jenkins contributes to many educational programs and symposia for government, non-government organisations and the pharmaceutical industry. She is a member of national and international advisory boards and steering committees for AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim and Novartis.

Q:

SELF-TEST QUESTIONS

True or false?

1. High doses of inhaled corticosteroids increase the risk of pneumonia in patients with chronic obstructive pulmonary disease.
2. If a patient with chronic obstructive pulmonary disease needs to use a short-acting bronchodilator several times a week, an inhaled corticosteroid should be added to their treatment.

Answers on page 41

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ARTICLE

Medication charts in residential aged-care facilities

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Keywords
aged, medication errors, National Residential Medication Chart

Aust Prescr 2017;409:20–2
http://dx.doi.org/10.18773/austprescr.2017.004

SUMMARY

An aged-care facility should maintain a current, accurate and reliable record of the drugs prescribed and given to a resident. The correct use of a medication chart can meet this requirement.

The hard-copy National Residential Medication Chart aims to provide a standard form for the prescription, dispensing and administration of drugs. In addition to providing a comprehensive record, it should facilitate communications between health professionals who are unlikely to visit aged-care facilities at the same time.

The chart will also enable pharmacists to supply most drugs without the need for a separate prescription. This should reduce transcription errors and avoid delays in the supply of medicines.

There are concerns about the efficiency of using the chart. These could possibly be addressed if an electronic version was developed.

Introduction

A medication chart in a residential aged-care facility serves as a communication tool between doctors, nurses, pharmacists, other health professionals and hospitals regarding a resident's medicines. It is used to direct how and when drugs are to be administered and as a record of their administration.

There are almost 3000 aged-care facilities in Australia with approximately 200 000 residents.[1] With an average of 9.75 medications per resident, polypharmacy (defined as the concurrent use of five or more drugs) is widespread.[2] The Department of Health has published 'Guiding principles for medication management in residential aged care facilities'.[3] This states that 'facilities should ensure all residents have a current, accurate and reliable record of all medicines selected, prescribed and used, to support safe prescribing and administration'. The correct use of an appropriately designed medication chart, either hard copy or electronic, addresses this requirement.

Most facilities use proprietary printed medication charts available from commercial printers, aged-care service companies, or electronic versions from agencies whose charts are able to be printed on site.

Issues with medication charts in residential aged care

The proprietary printed charts used in aged-care facilities are usually multiple-page booklets designed to last for periods of up to six months. Whereas patients, doctors, nurses and pharmacists are usually co-located in hospitals and can physically use the same chart, this is not the case in residential aged-care facilities. Their differing locations result in all paperwork needing to be copied and faxed or shared electronically between the facility, doctors and pharmacists. The multiple-page booklet format of the charts used in aged care complicates transmitting a comprehensive record of a resident's current treatments.

Drugs can be supplied to residents of aged-care facilities in original packs dispensed by a pharmacist and labelled with instructions for administration or supplied in dose administration aids. These aids may be packed with a single drug per pack (unit dose) or with a number of drugs due to be simultaneously administered to the resident (multi dose). While dose administration aids have become common place in aged-care facilities, not all prescribed drugs can be packed together due to formulation, stability or regulatory restraints. This frequently results in the use of parallel supply systems of original packs and dose administration aids.

All jurisdictions require a registered or enrolled nurse to be responsible for the drugs given in a residential aged-care facility. However, in some circumstances, trained nursing assistants are able to help residents to self-administer medicines.[4] If supplied in an original pack, the nurse who administers a drug is required to verify it against the doctor's order, select the correct quantity and record the administration on the chart. If the drug is supplied in a dose administration aid, the staff member who assists a resident to self-administer or who administers the contents must sign for doing so without the responsibility of identifying each drug.

Medication charts need to be able to accommodate these differences in packaging and the obligations for documentation.

Any scheduled drug ordered on a medication chart in a residential aged-care facility requires a separate prescription to be written to facilitate supply and, if the medicine is listed on the Pharmaceutical Benefits Scheme (PBS), to enable reimbursement of the pharmacist. There are risks associated with the duplication of a written medication order. There are also additional 'clerical' obligations and a potential for a delay in treatment. Any tardiness in writing a complete prescription may entail a delay in supply or payment and, if the prescription is never written, there will be no reimbursement of the cost.

Electronic advances

Studies have shown that the implementation of electronic medication management systems which link residential aged-care facilities with prescribers and pharmacists improves clarity and accuracy, provides efficiency and enhances safety.[5,6] The systems were developed as tools to record and report on drug administration, but now include sharing of real-time data on adherence and changes to treatment, and the ordering of stock. The electronic version of the doctor's order displays just the current drugs resulting in a much simpler document than the proprietary printed charts. Administration sign-off can be paper-based or completed electronically.

The National Residential Medication Chart

The fifth Community Pharmacy Agreement between the Department of Health and the Pharmacy Guild of Australia funded the development of a system for supply and claiming of PBS medicines from a standardised medication chart in residential aged-care facilities without the need for a separate prescription.[7] This initiative was intended to reduce the administrative burden for prescribers, pharmacists and staff by improving the timeliness of prescribing and dispensing and minimising the duplication of effort for the resident's healthcare team.[7] The concept should enhance medication safety by reducing the risk of transcription errors that arise from the need to write drug orders twice – once on the chart and again on the prescription.

The Australian Commission on Safety and Quality in Health Care was engaged to develop a medication chart that would incorporate the required data.[8] This project was informed by the long-standing work of the Commission in developing the National Inpatient Medication Chart and supplementary charts. These are a nationally consistent set of paper-based medication charts (with some available in an electronic format), which aim to enhance patient safety through the widespread use of standard, evidence-based charts.[9,10]

The development of the National Residential Medication Chart addressed the sections, layout, functionality and duration of the chart. Evaluation in 22 aged-care facilities demonstrated significant reductions in medication administration errors and less incorrect packaging of residents' medicines.[11]

Legislative changes have been made in all jurisdictions enabling the use of a compliant medication chart, such as the National Residential Medication Chart, for prescribing, dispensing and claiming purposes. The National Residential Medication Chart is at this stage paper-based, however there is potential for software providers to develop an electronic option.

Format

The National Residential Medication Chart is a 52-page landscape format booklet that includes sections for patient and practitioner identification, resident assessment, allergy, weight and blood glucose documentation.[12] It is intended to last for four months. Space is provided for ordering and recording the administration of 11 regular drugs, eight short-term drugs, six 'when-required' drugs, three nurse-initiated medicines and six phone orders. There can be three warfarin orders (or other variable dose drugs) with related pathology instructions and results, three regular insulin orders and four 'when-required' insulin orders. The chart also includes space for recording nutritional supplementation and supply to residents from dose administration aids.

Supporting information printed on the National Residential Medication Chart includes instructions on the use of the chart, common abbreviations, advice regarding PBS regulations and checklists for the safe administration of drugs. Colour has been used extensively to differentiate sections of the chart.

If an order is written on the National Residential Medication Chart in accordance with the regulations, the majority of PBS-listed drugs can be dispensed without the need for a separate prescription. However, a prescription is still required for PBS Authority items requiring prior approval, PBS Section 100 items, controlled drugs (Schedule 8 medicines) and extemporaneously compounded medicines.[8]

As the order for a drug written on the National Residential Medication Chart is for both administration and supply, the doctor is required to include a start date and an indication of the duration of treatment. Streamlined authority code, 'Closing the Gap' identification and brand substitution are required if applicable.[8]

Implementation

The National Residential Medication Chart incorporates some of the medicine safety principles of the National Inpatient Medication Chart. However, the desired safety and efficiency outcomes will only be achieved if residential aged-care facilities and health professionals find the National Residential Medication Chart easy to use. Practitioners, and companies printing drug therapy charts, report that there has been limited implementation of the National Residential Medication Chart. This may be due to factors identified by residential aged-care staff, including:

- increased medication round times as a result of having to move back and forward through the many pages and different sections of the chart
- increased potential to miss drugs or a change of dose if they are written in different sections
- the cost of printing a chart incorporating many colours
- the time to communicate changes to the pharmacy as a result of needing to copy and fax a minimum of 12 pages
- the need for doctors to handwrite all entries, including sections required by the PBS that would otherwise be generated automatically in their prescription software
- the need for doctors to rewrite the whole chart every four months
- the need for pharmacists to maintain a copy of at least 22 pages of the chart, access the correct page in order to record ongoing dispensing of an item, annotate the copy with details of each item dispensed, cease PBS dispensing when the chart is four months old, and continue to access hard-copy PBS scripts for specific drugs.

Some of the identified factors are not specific to the National Residential Medication Chart and relate to changes in practice associated with the new format and processes. Due to the range of health professionals and the significant changes involved, implementation of the National Residential Medication Chart requires a detailed change management process. The Australian Commission on Safety and Quality in Health Care has prepared user guides for staff and health professionals.[8]

Conclusion

Some of the inefficiencies and risks associated with the ordering and supply of drugs in residential aged-care facilities, arising from the external location of doctors and pharmacists, are resolved by the capacity to work from a single data source in the form of the National Residential Medication Chart. Problems associated with implementation of the chart may be due to both the format of the chart and the change in practices associated with its use. An electronic version of the National Residential Medication Chart may address the operational problems that have been noted with the introduction of the paper version. <

Elspeth Welsh is employed by Epic Pharmacy which provides services to residential aged-care facilities. At the time of writing John Jackson was also employed by Epic Pharmacy.

John Jackson was a member of the Australian Commission on Safety and Quality in Health Care advisory committees for the National Residential Medication Chart program and has been involved with committees which developed and maintain the National Inpatient Medication chart and related charts.

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ARTICLE

Midazolam for status epilepticus

SUMMARY

Midazolam is now the first-line treatment for status epilepticus in children.

The drug can be given via several different routes. Transmucosal administration is safe, effective, easier to use and more socially acceptable than rectal diazepam.

The aim is to stop convulsive seizures that have lasted longer than five minutes as soon as possible.

Transmucosal pre-hospital administration by carers is recommended for patients with a predilection for prolonged seizures, or those with limited access to emergency services. This reduces the time to treat and improves outcomes.

General practitioners can obtain midazolam through the Prescriber Bag Drug Supplies section of the Pharmaceutical Benefits Scheme. For pre-hospital use, 5 mg in 1 mL plastic ampoules is recommended.

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Keywords
Doctor's Bag, emergency drugs, midazolam, Pharmaceutical Benefits Scheme, status epilepticus

Aust Prescr 2017;40:23–5
http://dx.doi.org/10.18773/austprescr.2017.005

Introduction

Midazolam is a benzodiazepine which has been used in the treatment of status epilepticus since the early 1990s. Midazolam has replaced diazepam as the preferred first-line drug for acute management of seizures in infants and children. It is not currently registered for this indication in Australia, but in 2015 midazolam was made available for emergency use by GPs through the Pharmaceutical Benefits Scheme and is widely used off label for the treatment of seizures. Midazolam may also be administered by parents and carers at home and school, by ambulance officers and in the emergency department.

Treating status epilepticus

Most convulsive seizures do not last longer than five minutes and resolve without medical intervention. Any convulsive seizure lasting longer than five minutes should be treated as there is an increased risk of neuronal compromise following prolonged seizures.[1]

Drugs, such as midazolam, are used to abort ongoing seizures and thereby avoid the complications of prolonged status epilepticus. The drugs resolve the majority of emergency presentations and they work best if given soon after the seizure has exceeded five minutes. Drug treatment becomes less effective if the seizure lasts longer than 15 minutes.[2] Repeat doses may be effective but increase the risk of complications and sometimes inappropriately delay administration of second-line therapy.

First-line drugs

For many years, intravenous or rectal diazepam was the first-choice drug for stopping status epilepticus. It is effective but can be difficult to use, and rectal administration was less socially acceptable outside hospital.

Midazolam is a water-soluble benzodiazepine which can be given intramuscularly, intravenously or transmucosally. It was incorporated into a guideline for the management of seizures published by the New South Wales (NSW) Ministry of Health in 2009.[3] The 2016 version of this guideline says that midazolam is the drug of first choice when intravenous access has not been obtained.[4] Administering midazolam outside hospital reduces the time-to-treat period and improves outcomes.[5] Midazolam can also be used to terminate clusters of brief convulsive seizures and manage bouts of non-convulsive status epilepticus.

Second-line drugs

Established second-line drugs include phenytoin, phenobarbitone and levetiracetam. These are given after transfer to an emergency facility if first-line drugs fail to stop the seizures.

Emergency use of midazolam

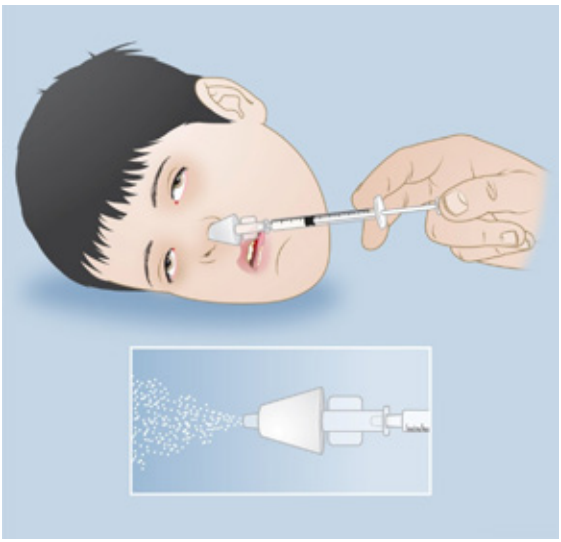
The aims of giving midazolam are to avoid progression to, and the complications of, convulsive status epilepticus. Early treatment improves outcomes and avoids complications.

Plastic ampoules of 5 mg in 1 mL (containing approximately 18 drops) are easier to use than the

Fig. 1 **Technique for administering buccal midazolam**

Reproduced with permission. The Royal Children's Hospital, Melbourne, Australia; Kids Health Info; www.rch.org.au/kidsinfo

Fig. 2 **Technique for administering intranasal midazolam**



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glass ampoules. They should be protected from light, kept in their foil wrapper until required and stored at 15–25° C.

Current guidelines recommend an initial buccal or intranasal dose of 0.3 mg/kg to a maximum of 10 mg.[4] Each drop of the 5 mg/mL solution contains approximately 0.3 mg midazolam. Absorption takes approximately 1–3 minutes and midazolam can take up to 10 minutes to abort the seizure. The dose can be repeated after five minutes if seizures persist. The techniques for administration are described on the websites of the Royal Children's Hospital Melbourne[6,7] and the Paediatric Epilepsy Network NSW[8] (see Figs 1 and 2).

Ambulance officers and paramedics in NSW use midazolam in single or repeated doses of 0.15 mg/kg intramuscularly or intravenously for children in convulsive status epilepticus. They can give adults cumulative 2.5–5 mg intravenous doses of up to 15 mg in total.[9] Emergency departments follow the relevant state guidelines for children and adults with midazolam as the first-choice therapy.[3,10]

Administration by carers

When used in the community midazolam can reduce hospital admissions for children with complex epilepsy.[11] Providing a supply of midazolam to a parent or carer can be considered for children (and dependent adults) who have convulsive seizures which frequently last more than five minutes.

Parents and carers can be anxious about giving midazolam so training is needed. Education is available from specialist epilepsy nurses and can be arranged through patient support organisations such as Epilepsy Action (www.epilepsy.org.au) and Epilepsy Australia (www.epilepsyaustralia.net). Prepare clear concise directions for administration. A suitable administration template can be found on the Paediatric Epilepsy Network NSW website.[8]

Safety and tolerability

The common adverse effects of transmucosal midazolam are sedation, ataxia, irritability or euphoria, and mild respiratory depression. Intranasal administration may also produce local irritation, stinging, sometimes with eyes watering and a runny nose.

Avoid using the intranasal route in children with any awareness during seizures because of the irritation. We recommend using a reusable mucosal atomisation device for intranasal administration, delivering half the dose into each nostril. Mucosal atomisation devices may be available through hospitals or the ambulance service and can be purchased privately.

Major complications of treatment are unlikely when the guidelines for midazolam are followed.[12] With a single dose, respiratory depression is rare. Cumulative subsequent doses are much safer if given where expert airway support is available.

When midazolam is provided for use by carers, we recommend nominating only one prescriber

and one dispenser for each child in order to avoid confusion. This is most often the treating neurologist and the hospital pharmacy because of the restricted availability of the plastic ampoules. Midazolam is available in a range of concentrations and volumes so we restrict prescription to 5 mg in 1 mL plastic ampoules, wherever possible, to avoid dosing errors. Having a single prescriber and dispenser also reduces the potential for abuse and stockpiling. In a review of four years of pre-hospital use we found only two out of 197 families with circumstantial evidence of carers abusing the drug.[13]

Parents used to using plastic ampoules may struggle without extra instruction if glass ampoules are dispensed. It is always best to review parental understanding and techniques periodically. Frequent problems include:

- loss of dose from 'salivary washout' in dribbly children
- dose swallowing in partially aware children
- blocked noses
- confusion between 'mL' and 'mg' and the risk of accidental overdosing
- failure to adjust doses for growing children.

Conclusion

Midazolam is a benzodiazepine which is now the recommended first-line drug for treating convulsive status epilepticus. When used according to guidelines for infants, children and adults it appears safe and effective.

The use of midazolam by carers in the community is a widely accepted but off-label practice. It must be carefully planned, supervised and controlled. <

Conflict of interest: none declared

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ARTICLE

Should pulse pressure influence prescribing?

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Keywords
atherosclerosis, blood pressure, cardiovascular disease

Aust Prescr 2017;40:26–9
http://dx.doi.org/10.18773/austprescr.2017.006

SUMMARY

The pulse pressure is the difference between the systolic and diastolic blood pressure. It is influenced by the stroke volume and vascular resistance.

As people age the walls of their arteries become stiffer. This increases the pulse pressure.

A high pulse pressure may be associated with reduced coronary perfusion. It may therefore be a predictor of future cardiovascular events, but this has not been confirmed by meta-analysis.

There are no drugs specifically aimed at reducing arterial stiffness. Treatment should be aimed at systolic and diastolic pressure rather than reducing pulse pressure.

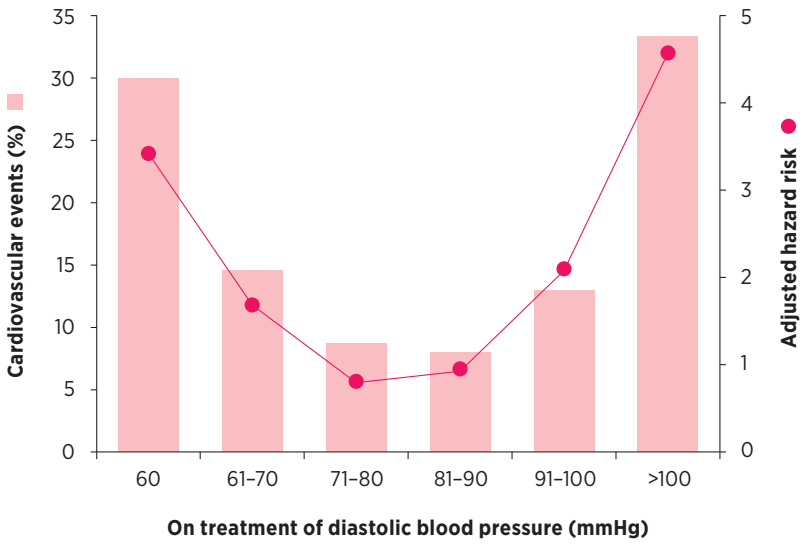
Introduction

Cardiovascular events are more likely in patients with high blood pressure, but low blood pressure may also increase the risk. This J-shaped curve has been seen in some studies of antihypertensive drugs for both systolic and diastolic blood pressures (see Fig.)[1,2]

The pulse pressure is the difference between the systolic and diastolic blood pressure. Classically, a wide (high) pulse pressure is a sign of aortic valve regurgitation and a narrow (low) pulse pressure is a sign of aortic stenosis. In the absence of valvular disease, a high pulse pressure may be a sign of stiffness in the arterial walls, and is a risk factor for coronary artery disease and myocardial infarction.

Many studies have identified pulse pressure as a predictor for future cardiovascular events. In some cases pulse pressure has appeared to be a better predictor than other blood pressure parameters. If pulse pressure is a predictor of mortality, the question arises as to whether altering the pulse pressure will improve clinical outcomes.

Fig. **J-curve for diastolic blood pressure**



J-curve for patients with coronary artery disease in the Treating to New Targets (TNT) trial[1]
Adapted from Reference 2

Physiology

The systemic arterial circulation consists of a pulsatile pump, the left ventricle, and a distributive arterial network comprising the aorta, large arteries and the microcirculation. As the pump is pulsatile, a haemodynamic description of the systemic circulation may be considered in terms of mean and pulse pressure. The mean arterial pressure is determined by cardiac output and peripheral vascular resistance, while the pulse pressure is the difference between the systolic and diastolic blood pressures.

The magnitude of the pulsatile component of the systemic arterial pressure largely results from the interaction between left ventricular stroke volume and the compliance of the arterial system, with possibly some additional contribution from wave reflection. Pressure waves travelling from the heart to the periphery may be subject to wave reflection. This is where the forward-travelling pressure wave is reflected back to the heart, particularly at points where the arterial circulation becomes narrowed. The magnitude and clinical significance of wave reflection is a topic of some uncertainty.

The compliance of the arterial circulation is defined as the increase in contained volume in response to pressure increase and results from the fact

that arteries are distensible. The degree of their distensibility varies throughout the circulation being highest in the proximal aorta which therefore has the greatest compliance in the arterial circulation.

The magnitude of large artery compliance is a function of arterial geometry (mainly diameter) and the properties of the arterial wall, predominantly wall stiffness. In healthy young people the wall is not stiff and therefore 'buffers' each left ventricular ejection. This limits the rise in systolic pressure and provides a supplemental pump to deliver blood flow during diastole. With ageing and certain diseases the large arteries become stiffer and progressively less able to provide the 'buffer' function. This results in a rise in systolic blood pressure and a decrease in diastolic blood pressure therefore widening the pulse pressure.

The acute response of large artery walls to increasing pressure is non-linear. As the blood pressure rises the walls become stiffer. A rise in mean pressure will therefore cause an increase in stiffness and a widening of pulse pressure. From middle age, a rise in pulse pressure is largely dependent on the degree of stiffness of the large arteries whereas in younger people it is largely a function of left ventricular stroke volume.

In addition to ageing, atherosclerosis increases the stiffness of large arteries. Increased arterial stiffness may thus be a surrogate marker for atherosclerotic vascular disease. A widened pulse pressure may be a marker for the extent of coronary disease. Measurement of pulse wave velocity (which increases with increased stiffness) has been proposed as a useful addition to risk assessment. (Pulse wave velocity refers to the transit time of the pressure wave, i.e. energy, and not mass movement of blood.)

Consequences of changing pulse pressure

The physiological consequences of stiffened large arteries may be related to both the rise in systolic blood pressure and the fall in diastolic blood pressure. The rise in systolic and pulse pressure may lead to further vascular damage and stiffness creating a deleterious feedback loop.[3] Experimentally enhanced pressure cycles have been shown to lead to accelerated vascular damage raising the possibility of a cyclical cause and effect whereby a stiffened vessel leads to amplified pulse pressure and further vascular damage.

In addition to the vascular consequences of elevated systolic pressure there is an increase in left ventricular afterload which may contribute to impaired left ventricular function. This may eventually result in an impaired capacity to generate the previously maintained stroke volume and hence an adequate pulse pressure. The relation between arterial compliance, stroke volume and pulse pressure is:

$$\text{pulse pressure} = \frac{\text{stroke volume}}{\text{compliance}}$$

A fall or rise in stroke volume at a given level of arterial compliance will therefore also affect pulse pressure.

The fall in diastolic pressure seen with pulse pressure widening may be particularly important for coronary perfusion since this occurs predominantly during diastole. In stenotic coronary arteries the reduced diastolic pressure could be expected to lead to impaired myocardial perfusion. Simultaneous measurements of blood pressure and ST segment depression in patients with angina showed a relationship between episodes of 'silent' ischaemia and immediately preceding hypotension noticeable at diastolic blood pressures below 65 mmHg.[4] This could explain the J-shaped relation between diastolic blood pressure and cardiac events in patients with coronary disease. Reduced perfusion is likely to be more relevant with a shortened diastolic duration (i.e. fast heart rate) and this may indicate the value of choosing therapy that will limit this reduction.

The J-curve is less evident for cerebrovascular disease. This could be because the cerebral vasculature is not dependent on diastolic perfusion.

Therapeutic targets

The compliant nature of the aorta and large arteries in healthy young people is due to extensive and ordered lamellae of elastin and a high elastin:collagen ratio. With ageing the elastic lamellae become fragmented and disrupted with a proportional increase in (cross-linked) collagen. This leads to a stiffer and less elastic arterial wall. A logical therapeutic strategy would therefore be to try to reverse or at least delay this structural change.

Researchers have studied molecules that would break the collagen cross links and thereby reduce vascular stiffness. The initial results were encouraging,[5] but the development of an effective drug has not progressed. Of the currently available drugs there was some evidence to suggest that ACE inhibitors and calcium channel blockers may have an effect on stiffness. However, any drug that reduces blood pressure will reduce arterial stiffness due to the non-linear stress–strain relationships of the arterial wall. Attributing changes in arterial compliance to direct effects on the large artery wall is therefore problematic.[6]

ARTICLE

Should pulse pressure influence prescribing?

Blood pressure as a predictor

The most complete evidence associating blood pressure and mortality comes from a meta-analysis of over one million people from 61 prospective studies.[7] An important aspect of this analysis was that only patients without known or evident cardiac or cerebrovascular disease were included. This means that it did not include individuals in whom a low diastolic pressure may be harmful. The analysis found that there was a continuous, strong and positive association between both systolic and diastolic blood pressure and cardiovascular events without any apparent lower threshold at least down to a pressure of 115/75 mmHg. The best predictors of outcome were 'mid' pressure (1/2 systolic + 1/2 diastolic) and mean pressure (2/3 diastolic + 1/3 systolic). Of the individual components systolic blood pressure was superior to diastolic blood pressure particularly in relation to cardiac disease. In contrast pulse pressure was only about half as predictive as systolic or diastolic pressure. There are no trials in which pulse pressure itself has been either a defined inclusion criterion or a therapeutic target but the prospective data used in the analysis do not suggest that treating pulse pressure, rather than systolic or diastolic blood pressure, in patients with no known cardiac or cerebrovascular events would be a logical approach.

A consequence of increased large artery stiffness is a widened pulse pressure. In such patients reduction of systolic blood pressure is an unambiguous goal. The Systolic Blood Pressure Intervention Trial (SPRINT),[8] in which patients either had or were at high risk of vascular disease, showed there was evidence that the target systolic blood pressure should be lower than current guidelines suggest. After one year, the intensive treatment group with a mean systolic pressure of 121.4 mmHg had fewer events than the conventional treatment group with a systolic blood pressure of 136.2 mmHg.[8] In patients with coronary stenoses there is the possibility that a lower diastolic pressure may be associated with more frequent and severe cardiac events. The mean diastolic blood pressure in the intensive arm of the SPRINT was 68.7 mmHg.

The relationship between blood pressure and cardiovascular events has also been examined in patients with known coronary artery disease, in the Treating to New Targets (TNT) trial[1] and International Verapamil-Trandolapril Study (INVEST).[9] Both trials found evidence of a J-shaped relationship most noticeably for diastolic blood pressure. In the TNT trial the curve relating diastolic blood pressure to events was relatively flat in the range 70–80 mmHg but there was a rise in cardiovascular events in the range 60–70 mmHg (see Fig.).[1,2] In INVEST a rise in events was evident in patients with systolic blood pressure below 110 mmHg and diastolic blood pressure below 70 mmHg. This association was more evident for diastolic blood pressure than systolic blood pressure and with a marked effect if the diastolic blood pressure was below 60 mmHg. The HOT study[10] did not find evidence of a J-shaped relation with diastolic blood pressure in patients with coronary heart disease. However, there was a non-significant rise in cardiovascular mortality below 75 mmHg when the 'optimal' diastolic pressure was in the range 80 to 85 mmHg.

There are other possible interpretations of a link between low diastolic blood pressure and cardiovascular events. A low diastolic blood pressure could be a consequence of impaired left ventricular function, however diastolic blood pressure remains a predictor of events after controlling for left ventricular function.[11]

Conclusion

At present there are no data from randomised clinical trials to support the concept that the reduction of elevated pulse pressure should be a therapeutic goal. While there are some observational data that pulse pressure is a superior predictor of events compared to individual measures of systolic blood pressure and diastolic blood pressure,[12,13] this is not supported by a large meta-analysis of people with no known cardiovascular events.

There is some evidence, and a plausible mechanistic basis, to suggest that a particularly low diastolic blood pressure is disadvantageous for patients with known coronary artery disease. In this group it would be prudent to avoid inducing excessively low diastolic blood pressure, especially if the patient has a fast heart rate. ◀

Acknowledgement: The author is indebted to Professor James Cameron, Director Monash Cardiovascular Research Centre, for his critical evaluation of the manuscript.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. A large pulse pressure may be a consequence of stiffness in the wall of large arteries

4. Pulse pressure is more predictive than systolic blood pressure of future cardiovascular events

Answers on page 41

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NEW DRUGS

New drugs

Cobimetinib

Aust Prescr 2017;40:30–1
http://dx.doi.org/10.18773/austprescr.2016.095
First published 12 December 2016

Approved indication: metastatic melanoma

Cotellic (Roche)
20 mg film-coated tablets
Australian Medicines Handbook section 14.2.5

Cobimetinib is another targeted drug for inoperable or metastatic melanoma. It should be used in combination with vemurafenib,[1] a BRAF inhibitor, and is indicated for patients with BRAF V600 mutations. About half of patients with metastatic melanoma carry these mutations.

Like trametinib,[2] cobimetinib is a MEK inhibitor. MEK1 and MEK2 are tyrosine kinases that interact with BRAF and lead to uncontrolled growth of melanoma cells. Adding a MEK inhibitor to a BRAF inhibitor has been shown to improve progression-free survival.[3]

The approval of cobimetinib is mainly based on a phase III trial of 495 previously untreated patients with advanced melanoma. The combination of cobimetinib and vemurafenib was compared to vemurafenib alone. Those with abnormal liver function, a recent history of acute coronary syndrome, congestive heart failure, active central nervous system tumours or retinal pathology were excluded from the trial. After a median follow-up of 7.3 months, median progression-free survival was significantly longer with cobimetinib and vemurafenib than with vemurafenib alone, and more people responded to the combination than to monotherapy (see Table).[4] Median overall survival was also significantly longer with the combination. After a median follow-up of 14.2 months, 48% of patients in the cobimetinib and vemurafenib arm were still alive compared with 38% in the vemurafenib arm.[5]

An earlier open-label, phase 1b, safety and dose-finding study of 129 patients with advanced melanoma found that people who had progressed on a BRAF inhibitor were less likely to respond to the combination of cobimetinib and vemurafenib compared with those who had never received a BRAF inhibitor (15% vs 87% had a complete or partial response).[6]

Serious adverse events (grade 3 or more) were common in the main trial and occurred in 71% of those taking the cobimetinib and vemurafenib combination and 59% of those taking vemurafenib monotherapy. Discontinuation because of an adverse event was similar between groups (13% vs 12%).[4]

Diarrhoea, nausea, elevated creatine kinase, decreased ejection fraction and retinal detachment were more common with cobimetinib and vemurafenib than with vemurafenib alone and are thought to be class effects of MEK inhibitors. Elevated liver enzymes, photosensitivity, fatigue, fever, bleeding and chorioretinopathy were also more frequently reported. Rash was very common in both treatment arms and was serious in 5–6% of patients. There were nine deaths from adverse events in the trial. Six of these were in the cobimetinib and vemurafenib group.[4]

Left ventricular ejection fraction may decrease during treatment therefore it should be evaluated at baseline and monitored regularly during therapy. Liver function tests should also be performed at baseline and monitored regularly. Creatine kinase may need to be checked during treatment. Patients with new or worsening visual disturbances should have an

Table **Efficacy of cobimetinib and vemurafenib in previously untreated patients with BRAF-mutated metastatic melanoma**

	Cobimetinib and vemurafenib	Placebo and vemurafenib
Number of patients	247	248
Median progression-free survival[4]	9.9 months	6.2 months
Response[4]		
complete	25 (10%)	11 (4%)
partial	142 (57%)	100 (40%)
Median overall survival[5]	22.3 months	17.4 months

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.

ophthalmologic examination as serous retinopathy can develop. Avoiding sun exposure and wearing sunblock when outdoors is also advised to reduce the risk of photosensitivity.

Adding cobimetinib to vemurafenib was associated with less cutaneous squamous cell carcinoma, keratoacanthoma and hyperkeratosis than vemurafenib alone.[4]

The recommended dose of cobimetinib is 60 mg taken every day for 21 days of a 28-day cycle. Following oral administration, the drug is extensively metabolised by cytochrome P450 (CYP) 3A and excreted in the faeces. Potent CYP3A inhibitors or inducers can affect cobimetinib concentrations and should not be co-administered.

Adding cobimetinib to vemurafenib improved progression-free survival by almost four months in patients with previously untreated inoperable or metastatic melanoma. Patients who had already progressed after taking a BRAF inhibitor were less responsive to this combination. Adverse effects were very common and some were serious so patient monitoring is important. Only patients with the BRAF V600 mutation qualify for this treatment.

T T manufacturer provided additional useful 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.

NEW DRUGS

Elbasvir/grazoprevir

Aust Prescr 2017;40:32–4
http://dx.doi.org/10.18773/austprescr.2017.010
First published 3 January 2017

Approved indication: hepatitis C

Zepatier (MSD)
tablets containing elbasvir 50 mg and grazoprevir 100 mg
Australian Medicines Handbook section 5.5

The management of chronic hepatitis C is rapidly changing, with newer regimens containing direct-acting antivirals without interferon.[1] This product is a fixed-dose combination tablet of elbasvir and grazoprevir indicated for people with hepatitis C genotypes 1 or 4.

Elbasvir inhibits the NS5A protein involved in the production and assembly of virus particles, and grazoprevir inhibits the NS3/4A protease involved in viral replication. After oral administration, peak plasma concentrations are reached within 2–3 hours. Steady-state concentrations are reached after six days of once-daily dosing. Almost all of the dose is excreted in the faeces as metabolites.

The approval of this combination is based on several trials in treatment-naïve and treatment-experienced patients infected with genotypes 1, 4 and 6. Studies included people co-infected with HIV, those with chronic kidney disease and people receiving opioid substitution therapy (see Table).[2-7] To be enrolled, patients had to have at least 10^4 IU/mL of hepatitis C viral RNA in their blood at baseline. Liver cirrhosis was allowed but those with decompensated liver disease were excluded from the trials.

The primary measure of effectiveness in the trials was the proportion of patients who achieved a sustained virologic response. This was defined as undetectable viral RNA in a blood test 12 weeks after the end of treatment (SVR12).

In the C-EDGE trial, which enrolled people who had not received previous treatment for hepatitis C, almost 95% of participants had a sustained virologic response to 12 weeks of treatment with elbasvir/grazoprevir.[2] Response rates were 92% (144/157) with genotype 1a, 99% (129/131) with genotype 1b, 100% (18/18) with genotype 4 and 80% (8/10) with genotype 6. Similarly high response rates were seen in treatment-naïve patients co-infected with HIV (C-EDGE CO-INFECTION).[3] In both trials, cirrhosis and high viral load at baseline did not seem to affect response rates.

Response rates to elbasvir/grazoprevir were high in patients who had failed on previous therapy with peginterferon/ribavirin (C-EDGE TE). Extending therapy to 16 weeks and adding ribavirin increased the response rate from 92% to 98%.[4]

Adding ribavirin to elbasvir/grazoprevir was also very effective in those who had failed previous therapy with peginterferon/ribavirin combined with boceprevir, telaprevir or simeprevir (C-SALVAGE).[5]

Another trial enrolled patients with stage 4 or 5 chronic kidney disease (C-SURFER) – 76% of participants were dependent on haemodialysis and 81% had stage 5 chronic kidney disease. After 12 weeks of treatment with elbasvir/grazoprevir, 94% had a sustained virologic response.[6]

In a trial of patients receiving opioid substitution therapy (C-EDGE CO-STAR), 92% had a sustained virologic response following a 12-week course of elbasvir/grazoprevir.[7]

Resistance to elbasvir/grazoprevir was observed in the trials. This was associated with single amino acid substitutions in the NS5A and NS3/4A proteins.

Fatigue, headache and nausea were the most common adverse effects in people taking elbasvir/grazoprevir,[2] including those co-infected with HIV[3] and those with advanced chronic kidney disease.[6] In patients who received the combination with ribavirin, anaemia was also common (14.8% of patients).[4]

Alanine aminotransferase elevations greater than five times the upper limit of normal occurred in 0.77% of patients given elbasvir/grazoprevir with or without ribavirin. Onset was generally eight weeks after starting treatment and usually resolved with ongoing therapy. Elevated bilirubin was also observed, often in those given ribavirin (6% of patients). Elbasvir/grazoprevir is contraindicated in moderate and severe hepatic impairment.

Both elbasvir and grazoprevir are partially metabolised by oxidation, primarily by cytochrome P450 (CYP) 3A, so there are numerous potential drug interactions. Strong inducers of CYP3A, such as the HIV drug efavirenz, phenytoin, carbamazepine and St John's wort, are contraindicated as they can reduce the concentrations of elbasvir and grazoprevir. Grazoprevir is also a substrate of OATP1B and co-administration with drugs that inhibit this transporter, such as cyclosporin and HIV drugs atazanavir, darunavir, lopinavir, saquinavir and tipranavir, may cause alanine aminotransferase elevations due to the increase in grazoprevir exposure. Interactions with other drugs may require dose changes and the product information should be consulted. For example, elbasvir/grazoprevir increases exposure to co-administered atorvastatin so the daily statin dose should not exceed 20 mg.

Table **Efficacy of elbasvir/grazoprevir with or without ribavirin in chronic hepatitis C**

Trial	Patient characteristics	Genotype	Treatment arm (duration)*	Efficacy – patients with SVR12
C-EDGE[2] (double-blind)	Treatment-naïve patients	1, 4, 6	elbasvir/grazoprevir (12 weeks)	94.6% (299/316)
C-EDGE CO-INFECTION[3] (open-label)	Treatment-naïve patients co-infected with HIV	1, 4, 6	elbasvir/grazoprevir (12 weeks)	96.3% (210/218)
C-EDGE TE[4] (open-label)	Previous treatment failure with peginterferon/ribavirin, with or without HIV co-infection	1, 4, 6	elbasvir/grazoprevir (12 weeks)	92.4% (97/105)
			elbasvir/grazoprevir+ribavirin (12 weeks)	94.2% (98/104)
			elbasvir/grazoprevir (16 weeks)	92.4% (97/105)
			elbasvir/grazoprevir+ribavirin (16 weeks)	98.1% (104/106)
C-SALVAGE[5] (open-label)	Previous treatment failure with peginterferon/ribavirin in combination with boceprevir, telaprevir or simeprevir	1	elbasvir/grazoprevir+ribavirin (12 weeks)	96.2% (76/79)
C-SURFER[6] (double-blind)	Stage 4 or 5 chronic kidney disease, treatment-naïve or experienced (previous treatment failure with peginterferon with or without ribavirin)	1	elbasvir/grazoprevir (12 weeks)	94.3% (115/122)
C-EDGE CO-STAR[7] (double-blind)	Treatment-naïve patients with or without cirrhosis receiving opioid substitution therapy	1, 4, 6	elbasvir/grazoprevir (12 weeks)	91.5% (184/201)

* elbasvir 50 mg and grazoprevir 100 mg given once-daily and ribavirin given twice-daily
SVR12 sustained virologic response 12 weeks after the end of treatment

The recommended elbasvir/grazoprevir dose for previously untreated patients or those who have relapsed since finishing a previous course is one tablet a day for 12 weeks. In patients who have had a null or partial response, or viral breakthrough during previous treatment, ribavirin should be added. This treatment should be given for 12 weeks in those with genotype 1b infection and for 16 weeks in those with 1a or 4 infection. Patients with severe renal impairment or end-stage renal disease should not be given ribavirin.

There have been no studies of the elbasvir/grazoprevir combination in pregnant women. Studies of high doses in rats and rabbits found no adverse effects on fetal development. It is not known if elbasvir and grazoprevir are excreted in human milk, however, in preclinical studies both drugs were excreted in lactating rats. No adverse effects were seen on nursing pups.

If ribavirin is added to elbasvir/grazoprevir, female patients and female partners of male patients must use contraception during and for six months after the end of treatment.

This fixed-dose combination of elbasvir and grazoprevir was very effective and generally well tolerated in people with chronic hepatitis C genotype 1 or 4. It seems to be suitable for people with HIV infection or advanced kidney disease. However, similar to paritaprevir/ritonavir/ombitasvir plus dasabuvir,[8] it is contraindicated in people with moderate to severe hepatic impairment. Other regimens such as ledipasvir with sofosbuvir[9] may be more suitable for these patients. The elbasvir/grazoprevir combination has numerous potential drug interactions, particularly with HIV medicines.

T T manufacturer provided additional useful information

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Mepolizumab

Aust Prescr 2017;40:35–6
http://dx.doi.org/10.18773/austprescr.2016.092
First published 14 November 2016

Approved indication: asthma

Nucala (GlaxoSmithKline)
vials containing 144 mg powder for reconstitution
Australian Medicines Handbook section 19.1.6

Some patients with asthma have severe disease that is not well controlled by inhaled treatments. They may require regular oral corticosteroids to control airway inflammation. In some patients there can be high concentrations of IgE which may respond to treatment with omalizumab. Other patients have high concentrations of eosinophils so these cells are potential targets for new drugs such as mepolizumab.

The life cycle of eosinophils is controlled by interleukin 5. This cytokine may be overproduced in patients with eosinophilic asthma. Mepolizumab is a humanised monoclonal antibody that binds to interleukin 5. This prevents interleukin 5 from binding to its receptors on the surface of eosinophils. A dose of mepolizumab will reduce eosinophils by at least 50%.

As mepolizumab is an immunoglobulin (IgG) it has to be given by injection. When reconstituted with water for injection, the powder forms a solution with a strength of 100 mg/mL. The usual dose is 100 mg injected subcutaneously every four weeks. After injection into the arm the bioavailability is 74–80%. The peak concentration is reached in 4–8 days and the terminal half-life following metabolism is 16–22 days. There have been no formal studies of hepatic or renal impairment or of drug interactions.

The Cochrane Airways Group has reviewed eight trials comparing mepolizumab with placebo in 1707 patients. Due to the heterogeneity of the studies the role of mepolizumab was uncertain, but it did reduce exacerbations and improve health-related quality of life in patients with severe eosinophilic asthma.[1]

One of the studies in the review randomised 621 patients with eosinophilic inflammation to intravenous infusions of placebo or mepolizumab 75 mg, 250 mg or 750 mg. Thirteen infusions were given at four-week intervals. Mepolizumab significantly reduced the numbers of eosinophils in the blood. There were 806 asthma exacerbations which required treatment with oral steroids. Compared to placebo the number of exacerbations per patient per year was reduced significantly by all doses of mepolizumab. For example, there was a 48% reduction with the 75 mg dose.[2]

A subcutaneous regimen was included in a trial involving patients with severe eosinophilic asthma who had experienced at least two exacerbations of asthma in the previous year. Treatment was given every four weeks for 32 weeks. There were 449 exacerbations. In the 194 patients assigned to receive mepolizumab 100 mg subcutaneously, the annual exacerbation rate was 0.83 compared with 1.74 in the 191 patients assigned to placebo.[3]

Another trial assessed whether subcutaneous mepolizumab can reduce the amount of oral corticosteroids consumed by patients with severe eosinophilic asthma. The 135 patients in the trial had been taking 5–35 mg of prednisone or equivalent for at least six months. After injecting mepolizumab or a placebo every four weeks for 20 weeks their use of corticosteroids was reassessed. The median reduction from their baseline dose was 50% for the patients taking mepolizumab. There was no reduction in the placebo group. The annual exacerbation rate was 1.44 with mepolizumab and 2.12 with placebo.[4]

Safety information is available for 1018 patients who took mepolizumab 100 mg subcutaneously. Common adverse events were headache and nasopharyngitis. Injecting an antibody can cause hypersensitivity reactions which may have a delayed onset. Approximately 6% of patients developed antibodies against mepolizumab. Injection site reactions affected 8% versus 3% of the placebo group. As eosinophils have a role in the immune response, mepolizumab may alter the response to parasitic infections. Although there were only a few cases of herpes zoster, two of them were serious. There is currently no information about the drug's safety in pregnancy, lactation or in children younger than 12 years.

The optimum use of mepolizumab is yet to be determined. Not all patients benefit, for example 36% were unable to reduce their dose of oral corticosteroid, withdrew from treatment or had a lack of asthma control.[4] Some of the patients suitable for treatment with mepolizumab may also qualify for treatment with omalizumab so the treatments should be compared. If a patient with severe refractory eosinophilic asthma is prescribed mepolizumab, how long should they take it for? A follow-up of some of the patients in the trials found that after stopping treatment there was a rise in eosinophil count and an increase in asthma symptoms and exacerbations.[5]

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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 European Medicines Agency and the Therapeutic Goods Administration.

Olaparib

Aust Prescr 2017;40:37
http://dx.doi.org/10.18773/austprescr.2016.093
First published 14 November 2016

Approved indication: ovarian cancer

Lynparza (AstraZeneca)
50 mg capsules

Olaparib is indicated as maintenance therapy for people with BRCA-mutated high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer. It is a poly (ADP-ribose) polymerase (PARP) inhibitor. In normal cells, DNA repair during cell division involves BRCA1 and BRCA2 proteins. In people who have mutations in BRCA1 and BRCA2 genes, DNA repair is mediated through alternative pathways and involves PARP enzymes. As olaparib inhibits PARP enzymes, it prevents DNA repair and causes the cancer cells to die.

Olaparib (400 mg twice daily) has been compared to placebo in a phase II trial.[1] The study enrolled 265 women with platinum-sensitive relapsed serous ovarian cancer with or without BRCA1 or 2 germline or somatic mutations. Patients must have previously had a complete or partial response to platinum-containing chemotherapy and at least two previous platinum regimens.

Progression-free survival was significantly longer with olaparib compared with placebo (8.4 months vs 4.8 months) but there was no significant difference in overall survival (29.7 months vs 29.9 months).[1] In a subgroup of 136 women with a BRCA mutation, progression-free survival was 11.2 months with olaparib and 4.3 months with placebo.[2] In an analysis of this subgroup, overall survival was 34.9 months in the olaparib arm and 30.2 months in the placebo arm. The difference was not statistically significant.[3]

The most common adverse events with olaparib included nausea (68.4% of patients), fatigue (48.5%), vomiting (31.6%), diarrhoea (22.8%), headache (18.4%), decreased appetite (18.4%), abdominal pain (17.6%), anaemia (16.9%), dyspepsia (16.2%) and dysgeusia (14%). These events were serious (grade 3 or 4) in some patients. Treatment-related events that led to permanent discontinuation with olaparib included palpitations and myalgia, erythematous rash and nausea.[1]

Haematological toxicity was common with olaparib and one patient in the trial died of haemorrhagic stroke associated with thrombocytopenia. Blood counts should be measured before starting treatment and then monthly for the first year of treatment.

Olaparib is genotoxic and should not be used during pregnancy. Taking it during lactation is also not recommended, although it is not known if the drug is excreted in breast milk.

Following oral administration, olaparib is rapidly absorbed and peak plasma concentrations are reached after 1–3 hours. As food slows absorption, capsules should be taken at least an hour after eating and two hours before the next meal. Olaparib is mainly metabolised by cytochrome P450 (CYP) 3A4 so concomitant use of potent CYP3A4 inducers or inhibitors, including grapefruit and Seville oranges, should be avoided.

Olaparib prolonged progression-free survival by 6.9 months in women with BRCA mutant-positive high-grade serous ovarian cancer. Overall survival was also slightly longer with olaparib than with placebo, although this difference was not statistically significant. Patients must have a confirmed BRCA1 or 2 mutation before starting treatment and have already had at least two courses of platinum-containing chemotherapy.

[X] manufacturer did not respond to request for data

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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, the European Medicines Agency and the Therapeutic Goods Administration.

NEW DRUGS

Talimogene laherparepvec

Aust Prescr 2017;40:38–9
http://dx.doi.org/10.18773/austprescr.2016.094
First published 14 November 2016

Approved indication: melanoma

Imlygic (Amgen)
vials containing 10^6 or 10^8 plaque-forming units/mL for injection

Talimogene is an oncolytic immunotherapy for melanoma consisting of genetically modified herpes simplex virus 1. It is indicated for intralesional treatment of cutaneous, subcutaneous and nodal lesions (after initial surgery) that cannot be surgically removed.

The pathogenicity of the virus has been attenuated by removing neurovirulence genes. These have been replaced by sequences encoding cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF). Once the virus is injected into a lesion, it is thought to multiply within cells and cause tumour lysis. The virus also causes local production of GM-CSF which is believed to stimulate the immune system to target melanoma cells. Talimogene can infect healthy cells but it is designed not to multiply inside them.

The approval of talimogene is based on a pivotal open-label phase III comparative trial with subcutaneous GM-CSF in 436 patients with inoperable stage III or IV melanoma. Those randomised to talimogene were given an initial dose containing 10^6 plaque-forming units (PFU)/mL. This was followed by a 10^8 PFU/mL dose three weeks later which was then continued every two weeks. Patients in the comparator group received recombinant GM-CSF 125 microgram/m^2 given subcutaneously every day for 14 days of a 28-day repeating cycle. Both treatments were continued for six months regardless of disease progression. Median duration of treatment was 23 weeks for talimogene and 10 weeks for GM-CSF. More patients had a durable response to talimogene than to GM-CSF (16.3% vs 2.1%). Median overall survival was also longer with talimogene than with the comparator (23.3 months vs 18.9 months) but the difference was not statistically significant (see Table).[1]

An earlier open-label, single-arm phase II trial in 50 patients with metastatic melanoma provided supporting data for the approval of talimogene. After a similar talimogene regimen was administered, 13 patients had a complete or partial response.[2]

The most common adverse events with talimogene were fatigue (50.3% of patients), chills (48.6%), pyrexia (42.8%), nausea (35.6%), flu-like illness (30.5%), injection-site pain (27.7%) and vomiting (21.2%). Most of these were mild to moderate.[1]

Impaired healing can occur at injection sites, particularly in those with underlying risks such as previous radiation treatment or lesions at poorly vascularised areas. Treatment-related cellulitis at the injection site was reported in 3.1% of patients. Talimogene can cause immune-mediated effects such as glomerulonephritis, vasculitis and pneumonitis. Worsening psoriasis and vitiligo have also been observed in patients during treatment.

As this drug contains live virus, it has the potential to cause disseminated herpetic infection in immunocompromised patients, such as those taking long-term, high-dose steroids. The drug is contraindicated in severely immunocompromised patients.

Table **Efficacy of talimogene for inoperable grade III or IV melanoma in a phase III trial**

Outcome	Talimogene (295 patients)	GM-CSF (141 patients)
Durable response rate*	16.3%	2.1%
Complete responses	32 (10.8%)	1 (<1%)
Partial responses	46 (15.6%)	7 (5%)
Median time to treatment failure	8.2 months (CI 6.5–9.9)	2.9 months (CI 2.8–4)
Median overall survival	23.3 months (CI 19.5–29.6)	18.9 months (CI 16–23.7)
Estimated survival after 4 years	33%	21%

* primary end point defined as the percentage of patients with a complete or partial response lasting for at least six months continuously and beginning within the first 12 months of treatment
CI confidence interval
GM-CSF granulocyte-macrophage colony-stimulating factor
Source: Reference 1

Patients treated with talimogene have been found to shed live virus. To avoid transmission, close contacts including family members, sexual partners and healthcare professionals should avoid direct contact with injected lesions and body fluids from the patient. In particular, patient contact with infants, pregnant women and people who are immunocompromised is not recommended. Patients should be warned that touching and scratching injection sites can spread the virus to other parts of the body. Suspected herpetic infections in patients or close contacts should be reported to the doctor.

There have been no studies on drug interactions with talimogene. However, co-administration of aciclovir and other antivirals could interfere with the efficacy of talimogene.

Numerous lesions can be injected at each treatment visit with the largest lesions injected first. The recommended injection volume depends on the size of the lesion. No more than 4 mL in total should be used at each consultation. Pregnant or immunocompromised healthcare providers should not handle or administer talimogene.

Although intralesional injections of talimogene were significantly better than subcutaneous GM-CSF for melanoma, the effect was modest with only 1 in 6 patients having a durable response. It is unclear why subcutaneous GM-CSF was chosen as the comparator in the main trial as there have been inconsistent results for this regimen in patients with melanoma.[3]

It is not known how talimogene will compare with other approved treatments for melanoma, such as pembrolizumab, nivolumab and ipilimumab.

[X] manufacturer did not respond to request for data

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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, the European Medicines Agency and the Therapeutic Goods Administration.

FEATURE

Valediction

Dr Anne Knight

Aust Prescr 2017;40:40
http://dx.doi.org/10.18773/austprescr.2017.009

Dr Anne Knight joined the Editorial Executive Committee in 2008. Based in Taree, New South Wales, Dr Knight brought a rural perspective to the deliberations of the Committee. This has helped to ensure that the information in *Australian Prescriber* provides practical advice for readers.

The editorial team has appreciated Dr Knight's great attention to detail. Her thorough analysis of the data supporting the new drug comments has significantly contributed to the accuracy of the information.

In 2014 Dr Knight became the chair of the Editorial Executive Committee. This was a particularly challenging time as the journal transitioned from print and online to its now fully digital format. The Editorial Executive Committee appreciates Dr Knight's commitment and support, and congratulates her on a job well done.

Correction

Correcting iron deficiency

Aust Prescr 2017;40:41
http://dx.doi.org/10.18773/austprescr.2016.096

The article by Jonathan Baird-Gunning and Jonathan Bromley on correcting iron deficiency (Aust Prescr 2016;39:193-9) has been corrected.

The Ferro-liquid line in Table 3 (Oral iron preparations) was incorrect. The Formulation should read Ferrous sulfate 30 mg/mL, not Ferrous sulfate, and the Elemental iron content should be 6 mg/mL, not 30 mg/mL.

A:

ANSWERS TO SELF-TEST QUESTIONS

1	True	2	False
3	True	4	False

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Typesetting by Stripe Design, Canberra
ISSN 1839-3942

Published by
NPS MEDICINEWISE

Independent, not-for-profit and evidence based, NPS MedicineWise enables better decisions about medicines and medical tests. We receive funding from the Australian Government Department of Health.