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CONTENTS

Editorial

Prescription drug subsidies in Australia and New Zealand

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Key words: cost of drugs, drug evaluation, drug regulation, Pharmaceutical Benefits Scheme.

(Aust Prescr 2010;33:2–4)

Australians and New Zealanders may see their systems for drug subsidy as different but, when viewed from the other side of the Pacific, important similarities emerge.[1] Both systems provide universal public subsidy to make commonly used medicines more accessible and affordable. This is still not achieved in some other OECD (Organisation for Economic Co-operation and Development) countries such as Canada and the USA.[2] Australia and New Zealand have, of course, different strategies for expenditure management, resulting in significant differences in expenditure. However the health outcomes obtained are likely to be similar. As contracting with drug manufacturers is becoming more common, the two countries appear to be converging in their use of certain policy tools.

Both Australia and New Zealand review the comparative cost-effectiveness of all new drugs before determining whether or not they will be subsidised. Few other countries in the world are as systematic in their application of evidence-based processes in providing access to medicines.

In this issue...

Information about adverse reactions to drugs will be returning to *Australian Prescriber* this year. The reporting of adverse events helps to improve practice. Kenneth Thomson and Dinesh Varma tell us that improvements to contrast media have enhanced patient safety. Knowing that some drugs' effects on the immune system can reactivate tuberculosis has led to recommendations for testing before prescribing. Anastasios Konstantinos discusses the tests which can be used when tuberculosis is suspected.

An increasing number of tests can now be done outside of a laboratory. Mark Shephard reviews some of the applications of point-of-care testing.

This review process is conducted by arm's-length committees in both countries – the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, and the Pharmacology and Therapeutics Advisory Committee in New Zealand (PTAC). A negative recommendation by these committees almost always means that the drug will not be listed (no means no), whereas a positive recommendation generally means that eventual listing will be subject to agreeable pricing terms (yes means maybe).

Despite comparable policy features, the approach to managing expenditure in Australia and New Zealand differs in some potentially important ways. One example is the co-payments for subsidised medicines. Both countries have lower fees for vulnerable patient populations. However, general patients in Australia face higher co-payments for each item (A$32.90) than their counterparts in New Zealand (up to NZ$15, depending on source of primary care). This difference may raise concerns about accessibility of medicines to the average Australian – drugs are subsidised but can patients afford them? It also may reflect differences in pharmaceutical benefits management – a subsidy system laid atop an otherwise free market in Australia versus a contracting system for managing purchases in the New Zealand market.

The Pharmaceutical Management Agency of New Zealand (PHARMAC), which was established in 1993, uses a capped national medicines budget, along with a variety of supplier contracts, to purchase medicines. The contracts include rebates on list prices, tendering for off-patent drugs, and bundle agreements where PHARMAC may list expensive new drugs in return for the manufacturer discounting the price of other products it supplies.

The effect of PHARMAC's approach on medicine expenditure in New Zealand compared to Australia, Canada and the USA is striking (see Table 1). Government spending on prescription drugs in Australia and New Zealand during 1993 was comparable (A$107 vs A$114 per capita). This is probably because before this point, Australia had used a relatively aggressive price negotiation program[3–5] and a

Table 1

Spending on medicines in Australia, New Zealand, Canada and the United States

Per capita expenditure on prescription drugs, A$ (PPP)

	Total			Government			Private		
	1993	2006	Change	1993	2006	Change	1993	2006	Change
Australia	$129	$462	260%	$107	$334	212%	$21	$128	498%
New Zealand	-	-	-	*$114	*$126	11%	-	-	-
Canada	$252	$750	198%	$117	$354	204%	$135	$396	193%
USA	$263	$1021	289%	$54	$348	550%	$209	$673	222%

Per capita expenditure on pharmaceuticals and other medical non-durables, A$ (PPP)

	Total			Government			Private		
	1993	2006	Change	1993	2006	Change	1993	2006	Change
Australia	$214	$609	184%	$107	$334	212%	$107	$275	156%
New Zealand	$221	$427	93%	$151	$285	88%	$70	$142	104%
Canada	$351	$901	157%	$117	$354	204%	$235	$547	133%
USA	$386	$1189	208%	$59	$360	510%	$327	$829	154%

PPP purchasing power parity

Figures are expressed in Australian dollars using the general purchasing power parity indices to convert currencies

* New Zealand data for public spending on prescription drugs. See: PHARMAC Annual Review 2006. Wellington: PHARMAC; 2006. www.pharmac.govt.nz/suppliers/reports/AnnualReview

Source: Calculations based on data from OECD (Organisation for Economic Co-operation and Development) Health Data 2008. www.oecd.org/health/healthdata

more systematically applied evidence-based coverage policy, whereas in 1993 New Zealand had only just established PHARMAC. From 1993 to 2006, growth in these costs was considerably slower in New Zealand compared to Australia (11% vs 212%). If over that period spending on prescription drugs in Australia had grown at comparable rates to New Zealand, expenditure in Australia during 2006 would have been about A$4 billion lower than it actually was.

PHARMAC's approach to expenditure management is considered aggressive by some and critics have questioned whether this approach requires a trade-off between expenditure management and patient access to drugs. Three levels of access need to be considered: access to a class of drugs, access to a specific drug within a class and access to various brand and generic versions of a specific drug.

There is little difference between Australia and New Zealand in the availability of subsidy for at least one drug within classes. Consider the leading five drug classes in the global marketplace – ACE inhibitors (including combinations), calcium channel blockers, proton pump inhibitors, HMG CoA reductase inhibitors (statins), and selective serotonin reuptake inhibitors. One or more treatment options from each of these drug classes are subsidised in Australia and New Zealand (see Table 2 online*).

While PHARMAC argued in 2006 that a broader range of drug types and formulations are listed in New Zealand than in Australia[6], we suggest that the system in New Zealand will result in fewer subsidised drugs listed within many drug classes than are listed in Australia. For the leading five drug classes, a total of 35 different drug types were listed on the Pharmaceutical Benefits Scheme (PBS), whereas 23 were listed by PHARMAC (Table 2 online). These differences may stem from PHARMAC's assessment of the relative value of adding newer drugs to established classes, such as esomeprazole to the list of proton pump inhibitors. Also, PHARMAC may have particular contracts that limit the number of drugs covered within a class in exchange for price concessions.

It is doubtful that the advantages (at the individual or population level) of allowing unfettered choice in established drug classes would outweigh the opportunity costs imposed on health systems. Differences in the choice of subsidised drugs within a class – whether in Australia, New Zealand, British Columbia, or a private insurer in the USA – have been the subject of considerable controversy for many years. In New Zealand, there is conspicuously little evidence that limiting choices is negatively associated with health outcomes. Limited research suggests that sweeping changes in drug availability (due to a therapeutic switching policy) may have

an impact on surrogate markers of health outcomes but little more.[7]

In contrast, there is substantial evidence to suggest that the more blunt policy instrument of patient co-payments may have detrimental effects on medicine accessibility and clinical outcomes.[8–10] 'Freedom of choice' under a drug benefit program may come at considerable cost to patients when escalating program expenditures produce a 'need' for patient cost-sharing policies.

Differences in the listings of subsidised drugs between countries may be shrinking as more drugs come off patent. Within a matter of years, virtually all of the 'blockbuster' drugs brought to market in the 1980s and 1990s will be off patent and therefore potentially available at prices that would justify unfettered subsidy – provided that the generic price is right.

Generic pricing differs quite considerably between Australia and New Zealand. Simply put, New Zealand widely uses tendering for drug products, whereas Australia does not. In New Zealand, this limits the choice between chemically interchangeable medicines, since only one version of the generic drug is subsidised. It also dramatically reduces the cost of acquiring off-patent prescription drugs.

In the five major drug classes, 81 different drug products are subsidised by PHARMAC compared to over 650 subsidised on the PBS (Table 2 online). Most off-patent drugs listed in New Zealand are from sole suppliers and deep price discounts are provided in exchange for exclusivity.

A common critique of tendering processes is that sole supply of generics may result in threats to medicine availability. While shortages are a potential risk that must be managed with tendering contracts (by including contingency and indemnity clauses), limiting national supply of an off-patent medicine to a single manufacturer is not unlike the sole supply arrangements for brand name manufacturers that are legally protected during the life of a patent.

The challenge in tipping the 'consumer choice' or 'expenditure management' scales in this debate will require a new form of social contract with retail pharmacy and, importantly, pharmacists. This will not easily be done, but it appears to be one of the (many) objectives underlying current PBS reforms.[11]

In an era of increasing generic availability, manufacturers launching new patented products into established therapeutic areas are struggling to find ways to avoid them being compared to older off-patent medicines. One way to protect a new product or class of products from this competition is to negotiate marketing contracts and pricing arrangements. Government drug plans potentially benefit from this desire to protect new products if it allows them to list more patented products while maintaining control over costs. As the trend toward contracting evolves, policy tools in Australia and New Zealand may begin to converge. From an outsider's perspective, one might expect these two countries to emerge (again) as exemplary cases for pharmaceutical benefits management.

Building on the evidence-based coverage processes established to date, leadership in the contracting era of pharmaceutical benefits management will require reasonable transparency of the process and evidence. Since these contracts effectively result in an undisclosed lower price for government drug plans based on certain volume or bundling arrangements, agencies will have to fight to keep only the most essential components of a contract confidential and ensure clinical data are made public.

Foremost, we hope that Australia and New Zealand do not let go of the fundamental principles that set their drug benefits schemes apart from other countries – a commitment to universal benefits and the systematic application of evidence-based decision making.

* Table 2 is available online with this editorial at www.australianprescriber.com/magazine/33/1/2/4

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Letters

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters referring to published articles may be sent to the author for response, and may be sent to an expert for comment. Letters are usually published together with any responses or comments. The Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

Influenza H1N1 vaccine

Editor, – We wish to comment on the New drugs section of *Australian Prescriber* in relation to H1N1 swine flu vaccine (Aust Prescr 2009;32:165–71). Even before launch, Australian consumers were asking for information on the vaccine. Readers may be interested in the depth and variety of questions asked of pharmacists operating Medicines Line (funded by National Prescribing Service – NPS). This national consumer telephone hotline provides information about prescription, over-the-counter and complementary medicines. Most (82%) of the 85 questions received between August and October 2009 related to vaccine safety. A representative sample of the questions is shown below.

Adverse effects and precautions

- Is the vaccine safe?
- Should I avoid it if I am allergic to another medicine (e.g. penicillin/pneumococcal vaccine)?
- Can it cause paralysis?
- What is anaphylaxis? I vomited after the vaccine.
- Can someone with Hashimoto's disease/pernicious anaemia/Guillain-Barré syndrome have the vaccine?

Interactions

- Can I have the vaccine while on my other medicines (e.g. phenelzine/warfarin/methotrexate/goserelin)?
- Are diphtheria and tetanus vaccine and the H1N1 vaccine safe together?
- Can my husband inject himself with darbepoetin the same day as getting his vaccine?
- Can I have the vaccine if I had oseltamivir five weeks ago?

Pregnancy and lactation

- Should I wait until after my baby is born to have my vaccine?
- Is it safe in first trimester/second trimester?
- How long after being vaccinated before I can breastfeed again?
- What are the risks and benefits of getting the vaccine while breastfeeding?

Administration

- Is the multidose vaccine really safe to use when you are the second or third patient?

Constituents

- Can I receive the vaccine if I have an allergy to egg protein/sodium benzoate/seafood/latex?
- Does the vaccine contain other substances such as bacteria/squalene/mercury/aborted human cells or monkey cells?

Efficacy

- Will the H1N1 strain in the vaccine be in next year's influenza vaccine?
- Will my prednisolone and azathioprine therapy reduce the effect of the vaccine?
- My wife comes in close contact with the public at work; should she get the vaccine?

Access to vaccine

- Does a travel medical centre provide the vaccine?
- When will a single dose vial be available?

Access to information

- Can you send me the consumer information leaflet?

Miscellaneous

- What are the legal implications of administering the vaccine to the public if they are otherwise fit and healthy?
- Can you give me unbiased information on the vaccine? The net has very misleading information.

By increasing awareness of our patients' vaccine concerns, health professionals are in a better position to proactively resolve consumer uncertainty and enhance compliance with the national vaccination strategy. If health professionals have difficulty answering questions on the vaccine, they can call the NPS Therapeutic Advice and Information Service (TAIS) on 1300 138 677.

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Point-of-care testing comes of age in Australia

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Summary

A wide range of point-of-care tests is available and being used in both hospital and community settings for acute and chronic illnesses. There have been significant improvements in device technology as well as advances in training methods, procedures to monitor analytical quality, and the electronic capture and management of test results from a central location. Various point-of-care tests have been found to be non-inferior to laboratory testing for managing chronic conditions in general practice and Aboriginal medical services. Maintaining the analytical quality of devices and ensuring that staff are properly trained are critical elements in sustaining a high quality point-of-care testing service.

Key words: clinical tests, general practice.

(Aust Prescr 2010;33:6–9)

Introduction

Point-of-care testing can be defined as pathology testing performed on-site during the patient consultation. It allows a rapid test result to be generated and used to make an immediate, informed clinical decision.

There have been significant technological and analytical advances in point-of-care testing devices and reagent manufacture. An increasing range of tests can now be performed on very small sample volumes in less than 10 minutes. These include tests for glucose, glycated haemoglobin (HbA1c), lipids, electrolytes, urea and creatinine, blood gases and coagulation and cardiac markers. The analytical performance of many point-of-care testing devices is equivalent to that of a laboratory and meets profession-derived analytical goals.[1,2]

Clinical applications

Point-of-care tests (both singly and in profile) are now available for acute and chronic situations and can be used for example in managing diabetes, warfarin requirements, electrolyte and acid–base disturbances and risk stratification of patients with suspected acute coronary syndrome. Table 1 lists examples of the more common biochemistry and haematological tests. Some tests such as haemoglobin and INR have both chronic and acute applications.

Table 1

Point-of-care tests for chronic and acute care

Parameters	Test
Chronic care	
Carbohydrate metabolism	Glucose
	Glycated haemoglobin
Lipids	Triglyceride
	Total cholesterol
	High-density lipoprotein cholesterol
	Low-density lipoprotein cholesterol (calculated)
Renal function	Urea
	Creatinine (estimated glomerular filtration rate)
	Urine albumin
	Urine albumin–creatinine ratio
Haematological/ coagulation	Haemoglobin
	INR
Liver function	Total protein
	Albumin
	Alanine aminotransferase
	Aspartate aminotransferase
	Gamma-glutamyltranspeptidase
	Alkaline phosphatase
	Bilirubin
Acute care	
Electrolytes	Sodium
	Potassium
	Chloride
	Total CO_2
	Anion gap
Arterial blood gas	pH
	Partial pressure CO_2
	Partial pressure O_2
	Saturated O_2
	Base excess
Cardiac function	Troponin I
	Troponin T
	Creatine kinase myocardial band
	Myoglobin
	N-terminal pro b-type natriuretic peptide
	Brain natriuretic peptide
Miscellaneous	
	C-reactive protein
	Ionised calcium

Glycaemic control

HbA1c remains the gold standard pathology test for long-term monitoring of glycaemic control in patients with diabetes. Devices measure HbA1c using either immunoassay or boronate affinity chromatography methods.

There are numerous strip-based testing devices for glucose monitoring. These generally measure whole blood glucose rather than plasma glucose, although newer devices can report a plasma-equivalent glucose concentration.

Blood lipids

Measuring blood lipids is useful for cardiovascular disease risk assessment and for managing patients on lipid lowering therapy. Testing devices measure a full lipid profile on capillary or venous blood. However, they calculate the low density lipoprotein (LDL) cholesterol using the Friedewald formula and cannot, as yet, determine LDL cholesterol directly as laboratories can now do.

Assessing renal function

Quantitative measurement of urine albumin or urine albumin–creatinine ratio is a key component in the review of patients with diabetes. Plasma creatinine measurement is currently the subject of an international standardisation, in which both laboratory and point-of-care testing methods are being aligned to an isotope dilution mass spectrometry reference method.

Warfarin monitoring

Point-of-care INR testing is becoming increasingly popular in general practice for monitoring patients on warfarin therapy.[3] Results can be linked with computer decision support software that automatically recommends the patient's next dose of warfarin.

Acute care

In an acute situation, electrolytes (including anion gap), blood gases and cardiac markers, notably troponin I or T, can be assessed. Some devices can measure these cardiac troponins down to the nanogram per mL range. Newer markers including brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-proBNP) remain expensive and their clinical utility continues to be debated.

Point-of-care testing models

In Australia, point-of-care testing is being used in the community as well as in hospitals particularly in rural and remote areas where access to laboratory services may be poor. There are now a number of working examples of innovative community-based point-of-care testing models that have improved clinical outcomes in both chronic and acute situations and are analytically sound (see box).

Managing point-of-care testing

A systematic approach is needed to organise and manage a sustainable and clinically effective point-of-care testing service.[4]

Models of community-based point-of-care testing

The national Quality Assurance for Aboriginal and Torres Strait Islander Medical Services (QAAMS) Program (www.qaams.org.au) provides glycated haemoglobin (HbA1c) and urine albumin–creatinine ratio testing for diabetes management in over 100 indigenous medical services across Australia.[2,5]

Queensland Health's statewide i-STAT network provides portable analysers throughout Queensland. These measure blood gases, electrolytes, coagulation, haematological and cardiac markers in critical care situations.[6]

The Integrated Cardiovascular Clinical Network SA (iCCnet SA) operates in rural South Australia (www.iccnetsa.org.au).

Physical requirements

Only a small area of dedicated bench space is required to conduct most point-of-care testing, as most devices are 'desktop' in size or smaller. Most devices require an AC power source although an increasing number of newer devices can work off battery power as well. Storage of reagents and consumables is generally at room temperature or 4º C, depending on the individual test.

Staff training

Training programs for staff who perform the tests (such as doctors, nurses and Aboriginal health workers) are required. The type and duration of training needed depends on the complexity of the device and the range of tests available, as well as the number of people being trained. For example, a training session for a simple device such as a glucose meter for a small number of trainees may take less than half a day, while regional training workshops for the Quality Assurance for Aboriginal and Torres Strait Islander Medical Services (QAAMS) Program, the largest national point-of-care testing program for diabetes management, take two full days for 20–30 trainees. Initial and ongoing training with competency assessment and updates are crucial for a sustainable high quality point-of-care testing service. Web-based training is now available for some Australian models.[2,5]

Analytical quality

A management system incorporating quality control and quality assurance processes adapted for non-laboratory settings is needed to continually ensure that the analytical quality of point-of-care testing results is appropriate for patient care.

The frequency of these checks depends on a number of factors including device complexity, size of the point-of-care network and the volume of patient testing at each site. For example, in the QAAMS program for diabetes management, quality control and quality assurance testing is performed monthly.[2] Should an abnormal result be obtained that does not fit the patient's clinical picture, the treating practitioner should repeat the point-of-care test and send the sample to the laboratory for confirmation of the result.

To sustain a point-of-care testing service, it is important to have ongoing technical support from the manufacturer of the device.

Test results

A further recent technological advance has been the capacity to send results electronically from multiple point-of-care testing devices to a central management point and from there to a clinical or hospital information system. This improved connectivity has enhanced the ability to develop large-scale point-of-care testing networks and streamline the delivery of testing services. Many Australian diagnostic companies provide connectivity software for their testing devices.

Is point-of-care testing effective?

There is a growing evidence base for the clinical, operational and economic effectiveness of point-of-care testing in hospitals and in the community.

Chronic care

For chronic care, there are published examples of how point-of-care testing can be an effective tool for improving control of chronic conditions either by reductions in HbA1c (for diabetes management)[7] or increased time in therapeutic or target ranges (coagulation studies).[3]

Acute care

The ability to perform tests such as potassium and blood gases by point-of-care testing in under five minutes on an acutely ill patient can inform initial management. For example, being able to measure potassium levels in a patient presenting with severe vomiting or diabetic ketoacidosis in a remote health centre is particularly useful. Similarly, the ability to rapidly stratify risk in patients with suspected acute coronary syndrome using supportive cardiac marker point-of-care testing can have benefits. These relate to reduced length of stay in emergency departments or reduced mortality through more rapid and effective risk stratification and treatment.[8,9]

General practice

A large randomised controlled trial of point-of-care testing in Australian general practice was commissioned by the Department of Health and Ageing.[10] As part of the trial, the effectiveness of point-of-care testing versus laboratory testing was assessed for managing chronic conditions in general practice. Data from 53 practices located in urban, rural and remote locations in Australia were analysed. Based on the primary outcome of percentage of patients with test results in the target range, point-of-care tests for HbA1c, urine albumin, albumin–creatinine ratio, total cholesterol and triglycerides were non-inferior to laboratory testing, but not for INR and HDL cholesterol.[11,12]

Limitations of point-of-care testing

While point-of-care testing may appear simple and easy to adopt, it is critical that health professionals seek the support of their local laboratory or specialist point-of-care testing service provider to support and maintain their service. These services may be helpful when selecting a device and with training and quality surveillance. The capacity to sustain a point-of-care testing service in a remote health service setting is often limited by high rates of staff (device operator) turnover.[13]

At present there is no Medicare rebate for point-of-care tests in general practice (other than a small group of mainly qualitative tests such as a pregnancy test). This limits the potential uptake of point-of-care technology and means a thorough cost–benefit analysis is needed before making the decision to implement point-of-care testing.

Conclusion

General practice and particularly rural and remote medical services are increasingly using point-of-care testing. Technological advances in device and reagent manufacture have now ensured that this type of pathology testing can be performed safely and effectively. It is convenient and accessible for the patient and allows immediate decision making for the doctor. Nonetheless, in implementing point-of-care testing, a significant commitment to operator training (particularly in the face of high staff turnover rates in remote areas) and surveillance of analytical quality are paramount.

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Adverse reactions and *Australian Prescriber*: back to the future

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The Australian Adverse Drug Reactions Bulletin was first published in 1974.[1] This monthly publication became colloquially known as the ADRAC Bulletin as its content was determined by the Adverse Drug Reactions Advisory Committee.

In 1975 *Australian Prescriber* was launched and the ADRAC Bulletin was incorporated into it. There was some initial disquiet about the merger as the rate of reporting of adverse drug reactions reduced. This fall may have reflected the change from monthly to quarterly publication of the Bulletin.[2]

The Adverse Drug Reactions section was a regular feature of *Australian Prescriber* until 1982, when the publication of the journal was temporarily suspended.[3] The Bulletin then resumed its existence as a separate publication. It remained separate when the publication of *Australian Prescriber* restarted in 1983.

Both publications were distributed using a government mailing list, but an *Australian Prescriber* survey in 1989 found that more than 25% of respondents were not receiving the publications.[4] This problem was mentioned in the Baume review of drug evaluation in 1991. The review recommended that the mailing list should contain at least all medical practitioners, pharmacists and dentists. This was because the Bulletin was recognised as the major means of informing health professionals about the analysis of adverse drug reaction reports.[5]

Shortly after the Baume review a decision was made to distribute the Bulletin in the same package as *Australian Prescriber*. Although there were concerns that this could affect the rate of reporting of adverse reactions, the joint mailing went ahead. This arrangement has continued until now, despite *Australian Prescriber* moving publishers.[3] In 1999 *Australian Prescriber* increased publication to six issues per year and the Bulletin followed in 2003.

From 2010, information about adverse reactions will once again be included in a special section of *Australian Prescriber*. Medicines Safety Update will be prepared by the production team of the former ADRAC Bulletin under the guidance of the new Office of Medicines Safety Monitoring (OMSM). As the electronic version of *Australian Prescriber* has many overseas readers, the new arrangements will deliver important information about adverse reactions to a wider audience.

Australian Prescriber is pleased to be part of the new direction for informing health professionals about adverse reactions to medicines.

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Medicines Safety Update No.1; 2010

Introducing Medicines Safety Update

This is the site for the new Medicines Safety Update from the Therapeutic Goods Administration (TGA). Medicines Safety Update will appear in each edition of *Australian Prescriber.*

Medicines Safety Update is replacing the Australian Adverse Drug Reactions Bulletin and will continue to bring you practical information and advice on drug safety and inform you about emerging safety issues.

Look here over the coming editions to find out about:

- the Advisory Committee on the Safety of Medicines (ACSOM) – this is the TGA's new expert advisory committee on medicines safety and replaces the Adverse Drug Reactions Advisory Committee (ADRAC)
- Medicines Risk Management Plans – what are they and how are they used?
- development of a new medicines alert system to replace the ADRAC Drugs of Current Interest Scheme
- regular articles about emerging safety issues.

A new era of medicines safety monitoring and communication of benefit–risk information at the TGA

The TGA, Australia's national regulator of therapeutic products, is responsible for ensuring that medicines, medical devices, blood, tissues and cellular therapies meet appropriate standards of safety, quality and efficacy and are made available to the community in a timely manner.

In keeping with international initiatives, the TGA is implementing some important changes to the way in which it monitors and manages the safety of medicines and communicates important benefit-risk information about medicines to its stakeholders.

Enhanced postmarket risk management – Risk Management Plans

In April 2009 the TGA formally adopted the European Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/ 96268/2005).

Adoption of this guideline means that applications for the registration of certain higher risk prescription medicines (new chemical entities, applications for paediatric use, new dosage forms, new routes of administration and significant extensions of indication) are now required to include a Risk Management Plan as part of the application.

The Risk Management Plan is meant to document not only what is known about the safety of the medicine at that particular point in time (termed the Safety Specifications), but also potential risks that require further elucidation, and how the sponsor intends to investigate those risks. The sponsor is required to establish a plan for monitoring the medicine when it is approved (a so-called Pharmacovigilance Plan) and consider whether there is a need for additional risk minimisation activities (such as additional prescribing and educational material, restrictions on promotion of and access to the medicine) and outline these in a Risk Minimisation Plan.

ACSOM – a new expert advisory medicines safety committee

A new expert advisory committee on medicines safety, called the Advisory Committee on the Safety of Medicines (ACSOM), has replaced ADRAC. This new committee exists as a statutory committee in its own right and has broader and enhanced terms of reference compared to ADRAC. A key role of the ACSOM will be the provision of expert advice to the TGA about the appropriateness of risk management plans and risk minimisation strategies for new high-risk medicines.

Improved access to prescribing and consumer information

The TGA is also committed to enhancing its dissemination of important benefit–risk information for medicines.

Legislation amendments enacted in 2009 have expanded the range of regulatory information the TGA may release, while protecting commercially sensitive and personal information. This will allow the TGA to publish on its website recommendations from external advisory committees and summary decision statements on evaluations of prescription medicines.

Over the next 12 months, the TGA will be progressively publishing a variety of documents on its website:

- **Product information (PI)** – this document contains a concise scientific summary of what is known about a medicine, targeted at healthcare professionals
- **Consumer Medicines Information (CMI)** – this document presents information about the use and safety of a medicine in lay language
- **Australian Product Assessment Report (AUSPAR)** – this document contains detailed technical and scientific assessments of the efficacy, safety and benefit–risk of the medicine undertaken by the TGA and the considerations that led the TGA to approve or reject an application. An AUSPAR will be prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extension of indications.

When this project is completed, the TGA website will provide a single point at which healthcare professionals, consumers and other interested parties can locate current, authoritative and reliable information about a medicine that is registered on the Australian Register of Therapeutic Goods (ARTG).

Hot news – experience with swine flu vaccine

Check out regular updates of suspected adverse reactions to the vaccine at:
www.tga.gov.au/alerts/medicines/h1n1vaccine1.htm

The Blue Card system is not changing

The cornerstone of medicines safety monitoring is spontaneous adverse event and incident reporting, so it's important that you continue to report adverse reactions to the TGA's Office of Medicines Safety Monitoring (OMSM).

The Blue Card system has been in operation for more than three decades and has resulted in more than 200 000 adverse drug reaction reports.

Anyone can report a suspected adverse drug reaction and the OMSM receives approximately 12 000 reports per year.

The Blue Card reporting form will continue to be distributed with the April, August and December issues of *Australian Prescriber.*

WHAT TO REPORT? (You do not need to be certain, just suspicious!)

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

- ALL suspected reactions to **new medicines**
- ALL suspected medicines interactions
- Suspected reactions causing
  - death
  - admission to hospital or prolongation of hospitalisation
  - increased investigations or treatment
  - birth defects

For blue cards

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ('blue card') which is available from the website: www.tga.gov.au/adr/bluecard.pdf or from the Office of Medicines Safety Monitoring, phone 02 6232 8744.

Reports can also be submitted:

online – go to the TGA website www.tga.gov.au and click on 'Report a problem' on the left
fax 02 6232 8392
email ADR.Reports@tga.gov.au

For further information from the Office of Medicines Safety Monitoring:
Phone: 1800 044 114 Fax: 02 6232 8392 Email: info@tga.gov.au

Diagnostic tests

Testing for tuberculosis

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Summary

Tuberculosis is caused by *Mycobacterium tuberculosis*. The approach to testing for tuberculosis depends on whether the aim is to diagnose active disease or latent infection. If active disease is suspected, it is important to identify the site of disease. Analysis of sputum specimens for mycobacteria should precede other tests. An infection should never be diagnosed as latent until active disease has been excluded. Tuberculin skin testing is recommended for diagnosing latent infection, but interferon gamma release assays may be useful in some circumstances.

Key words: diagnostic imaging, interferon gamma release assays, tuberculin skin tests.

(Aust Prescr 2010;33:12–18)

Introduction

Approximately 1000 new cases of tuberculosis (or TB) are diagnosed in Australia each year. Most of these patients were infected overseas and recent transmission within Australia is rare and limited to small clusters. Nevertheless, primary care clinicians need to remain aware of tuberculosis because early diagnosis and treatment prevents transmission.

Screening for latent tuberculosis is recommended before prescribing immunosuppressive therapy such as tumour necrosis factor alpha inhibitors, cancer treatment and transplantation. Patients with a high risk of tuberculosis reactivation (see Table 1), particularly those with HIV infection, should also be tested for tuberculosis.

Natural history of tuberculosis (Fig. 1)

Tuberculosis in humans is mainly caused by *Mycobacterium tuberculosis*. The infection is transmitted by respirable droplets generated during forceful expiratory manoeuvres such as coughing. Tuberculosis infection can be either active or latent. People with **active infection** have signs or symptoms caused by actively replicating tubercle bacilli. If this is in the lungs they are potentially contagious and usually have symptoms such as cough, chest pain, shortness of breath, fatigue, weight loss, fever and night sweats. Those with **latent infection** have previously been infected but have no symptoms or evidence of disease and are not contagious. However, they remain at risk of developing active tuberculosis (reactivation) during their lifetime.

Various factors are associated with an increased risk of becoming infected and subsequently developing disease (Table 1 and Fig. 1). Transmission is most efficient in poorly ventilated, crowded environments. Droplets become diluted once they enter the external environment and *M. tuberculosis* is rapidly destroyed by ultraviolet radiation.

Following lung infection, multiplication and dissemination of the organism is contained once cell-mediated immunity develops at 2–12 weeks. The risk of an individual progressing to active disease in the months and first few years after infection depends on the bacterial load and the effectiveness of their immune defences. A depressed immune response at the time of infection increases the risk for progressive primary (including disseminated) disease.

If someone is already infected, the risk for reactivation increases when their immunity is low. In the absence of reinfections, disease occurring more than 5–7 years after infection usually follows a decline in cell-mediated immunity, including age-related waning of cell-mediated immunity and iatrogenic immunosuppression (Table 1).

Diagnostic tests for tuberculosis

Various investigations can be used to help diagnose tuberculosis. These include medical imaging, microbiology tests, tests of a patient's immune response (tuberculin skin testing and interferon gamma release assays) and histopathology.

Chest radiology

If a patient has no respiratory symptoms, a normal chest X-ray almost excludes pulmonary tuberculosis. Chest X-rays are valuable for detecting pulmonary lesions of tuberculosis, however activity of disease cannot be judged with certainty.

Table 1

Risk factors for tuberculosis in Australia

Increased risk* of tuberculosis infection (i.e. increased risk of exposure to infectious tuberculosis)	Migrants from high tuberculosis prevalence countries
	Members of Aboriginal and Torres Strait Islander communities with high incidence of tuberculosis
	Healthcare workers
	Household contacts (particularly children) of people at increased risk for tuberculosis
Increased risk† of tuberculosis developing after infection‡	HIV infection
	Silicosis
	Diabetes mellitus
	Chronic renal failure/haemodialysis
	Gastrectomy/jejunoileal bypass surgery
	Organ transplantation requiring immunosuppression
	Carcinoma (particularly head and neck carcinoma)
	Immunosuppressive therapies (corticosteroids, cytotoxic chemotherapy, tumour necrosis factor alpha inhibitors)
	Malnutrition and low body weight (≥10% less than ideal)
	Infancy
	Older age

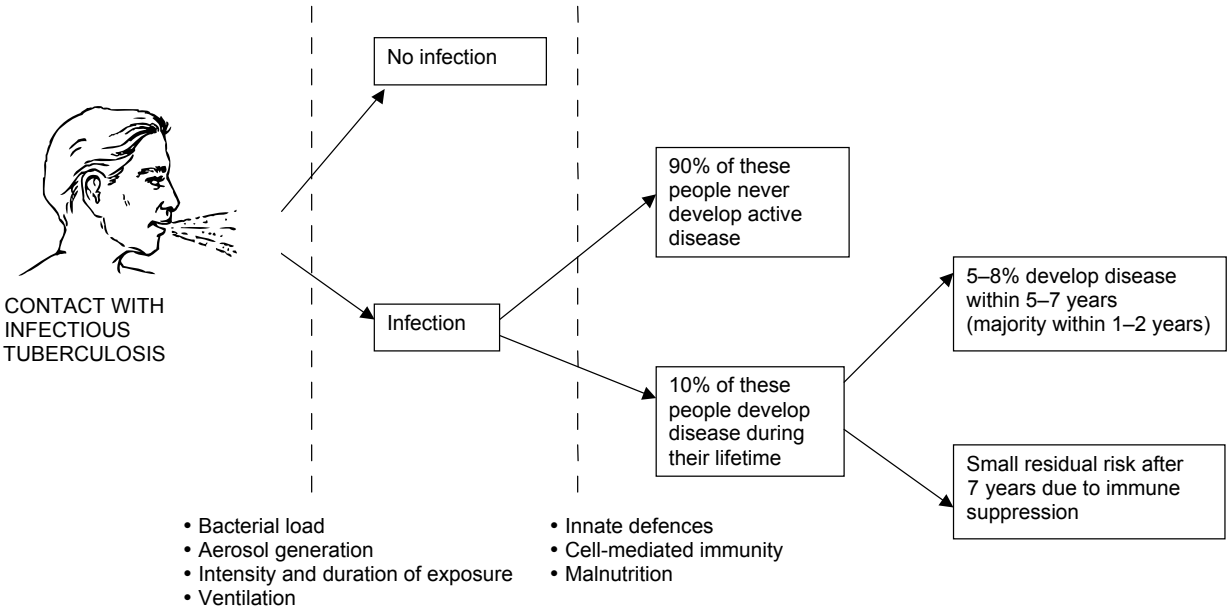
* In other countries, residents of institutions (prisons, nursing homes), homeless people, users of illicit intravenous and other drugs (especially when associated with HIV infection), and impoverished populations with limited access to medical services have high incidence of tuberculosis infection. In general, the risk for these populations has not been as great in Australia with the exception of Aboriginal and Torres Strait Islander populations.

† Most of this risk is related to cellular (T lymphocyte) immune defects.

‡ Patients with infections acquired within one year or with chest X-ray findings of fibrotic lung lesions consistent with untreated inactive tuberculosis have much greater risk of tuberculosis than those with tuberculosis infection acquired more than seven years previously.

Fig. 1

Natural history of tuberculosis in newly infected contacts



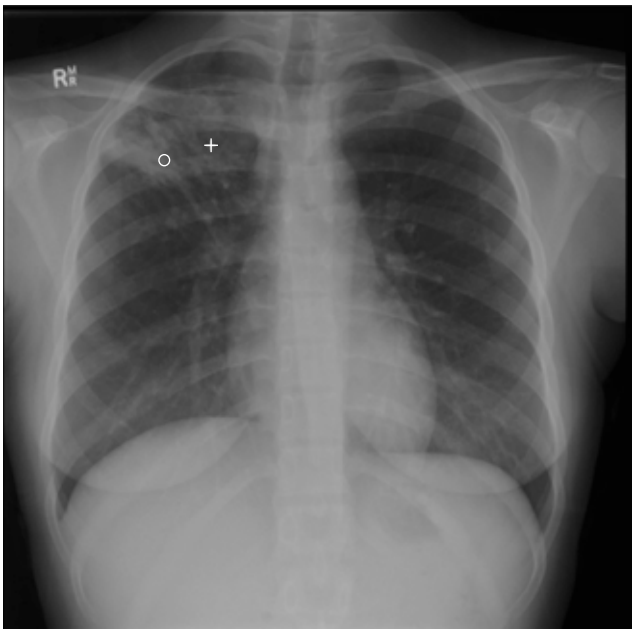
Classic upper zone chest X-ray changes (Fig. 2) can be due to other pathology, and pulmonary tuberculosis can have many other non-classic presentations with broad differential diagnoses. Unusual chest X-ray presentations (including normal chest X-ray) are more common in people with immune deficiencies and other comorbidities. Once pulmonary tuberculosis is suspected, the most appropriate initial investigation is sputum analysis and not further imaging, even if chest X-ray shows fibrosis which appears to be radiologically inactive.

Culture

Identifying *M. tuberculosis* remains the definitive means for diagnosis of active tuberculosis. Although culture of *M. tuberculosis* from a specimen is a sensitive test (75–80%), bacteria can take up to six weeks or more to grow. Collection of specimens should include three morning sputa whatever the suspected site of disease, unless chest X-ray is normal and there are no respiratory symptoms in a person with localised extrapulmonary disease.

Fig. 2

Chest X-ray showing pulmonary tuberculosis



Chest X-ray of an 18-year-old female who was part of a cluster of cases involving indigenous people in south-east Queensland and northern New South Wales. She presented with a history of cough for six months followed by weight loss, fevers, night sweats and fatigue. Sputum was smear-positive for acid-fast bacilli and grew *M. tuberculosis*. The X-ray shows an extensive infiltrate in the upper lobe of the right lung with air-space consolidation (note air bronchogram ○) and the formation of a number of cavities (+). There are surrounding reticulonodular satellite lesions and fibrosis of the involved lung with traction of the right upper hilum.

Smear microscopy and nucleic acid amplification

Mycobacteria retain certain dyes after being treated with acid and are classified as acid-fast bacilli. After collection, specimens can therefore be smeared on a slide, stained and visualised under the microscope. Although this technique, along with nucleic acid amplification, allows early identification it fails to detect many culture-positive cases. Nevertheless, microscopy for acid-fast bacilli rapidly identifies the most infectious tuberculosis cases and a positive sputum smear is sufficient for provisional diagnosis of tuberculosis.

When smears are positive for acid-fast bacilli, nucleic acid amplification of *M. tuberculosis* DNA can be used to rule out nontuberculous mycobacteriosis. This test has almost 100% specificity and sensitivity in acid-fast bacilli positive smears, with results provided within a few days (and potentially on the same day). While a negative nucleic acid amplification test of acid-fast bacilli almost excludes tuberculosis, the test can rarely be falsely negative in pulmonary tuberculosis (Fig. 3). Sputum smear-positive pulmonary tuberculosis is infectious so it is important to maintain infection control procedures while awaiting culture confirmation regardless of the nucleic acid amplification test result.

Screening for latent tuberculosis infection

The Australian National Tuberculosis Advisory Committee recommends tuberculin skin testing as the standard test for latent tuberculosis infection with targeted use of interferon gamma release assays (Quantiferon Gold) when high specificity is desired.

These tests have no role in initial investigations for active tuberculosis because negative results do not exclude disease and positive results may not necessarily indicate disease.

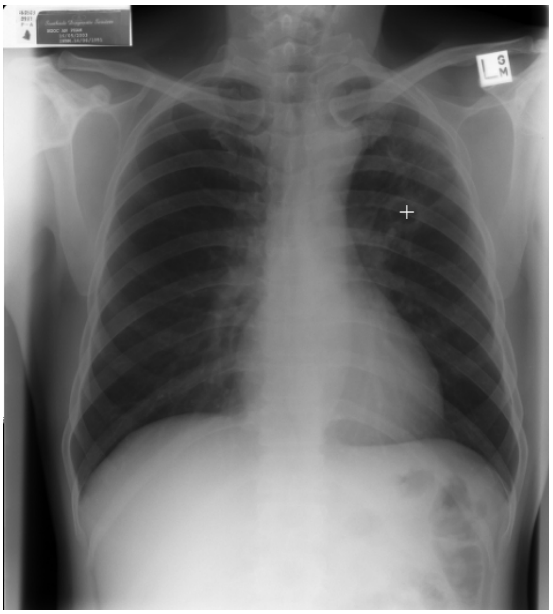
Tuberculin skin testing [1,2]

This test measures a patient's immune response to *M. tuberculosis* antigens (tuberculin). A small amount of tuberculin is injected intradermally and the skin reaction is measured two or three days later (Fig. 4).

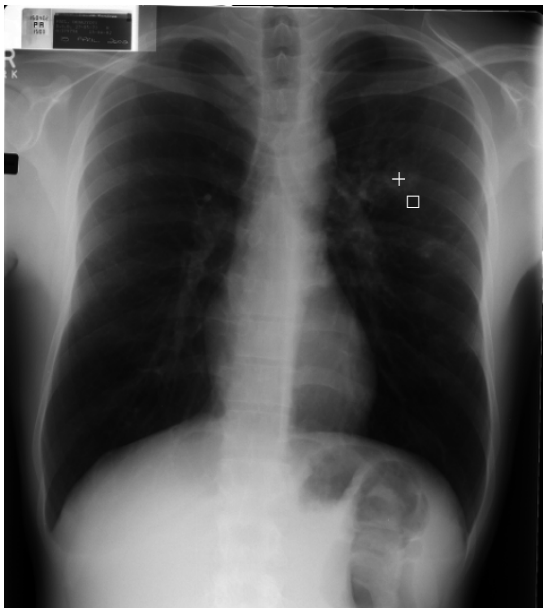
The test is very sensitive for detecting tuberculosis in healthy individuals if 5 mm induration is used to define a positive reaction. However, many conditions result in false negative reactions, including active tuberculosis (Box 1, part A). Bacillus Calmette-Guérin (BCG) vaccination and exposure to environmental nontuberculous mycobacteriosis cause intermediate size reactions (Box 1, part B). Sensitivity is often sacrificed by choosing larger indurations to define a positive reaction based on the incidence of tuberculosis and the extent of non-specific cross-reactivity in the population being tested. Box 2 provides general recommendations for categorising skin reactions, but regional tuberculosis control units should be consulted for local guidelines.

Fig. 3

Chest X-ray showing examples of sputum smear-positive tuberculosis with negative nucleic acid amplification test



A. Chest X-ray of 51-year-old male who arrived in Australia 15 years earlier from Vietnam. The X-ray was taken for investigation of unrelated shoulder pain and shows a cavity (+) adjacent to the left hilum. Sputum was smear-positive for acid-fast bacilli, however nucleic acid amplification was negative for *M. tuberculosis*. This was presumably because the organism lacked the IS*6110* DNA insert which was the target of the test.

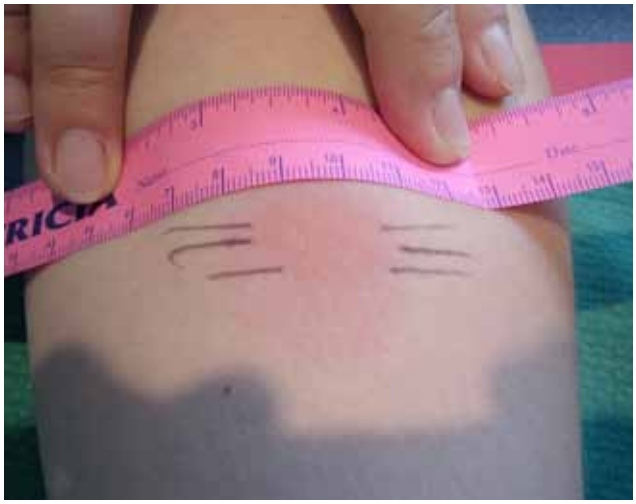


B. Routine chest X-ray taken for visa purposes in a 28-year-old university student from India. The X-ray showed a small cavity (+) with some surrounding infiltrate (□) adjacent to the left upper hilum. Initial sputum samples collected were smear-positive for acid-fast bacilli, but were repeatedly negative by nucleic acid amplification testing. Sputum samples were subsequently repeated. These specimens were more heavily smear-positive and tested positive for *M. tuberculosis* by nucleic acid amplification. The negative results were most likely due to a sampling error during collection of the first sputum specimen.

Fig. 4

Tuberculin skin testing, Mantoux method

A. Intradermal injection of tuberculin



B. Measuring induration 72 hrs later. Note: only the diameter of induration should be read, not the diameter of erythema.

Box 1

Factors that influence interpretation of tuberculin skin tests

A. Factors that may decrease skin reaction or give false negative reactions

- Infections
  - Viral (e.g. HIV infection, measles, mumps, chickenpox)
  - Bacterial (e.g. pertussis, brucellosis, leprosy, overwhelming tuberculosis, pleural tuberculosis)
  - Fungal
- Live virus vaccination (e.g. measles, mumps, polio)
- Metabolic disease (e.g. chronic renal failure)
- Malnutrition/protein depletion
- Lymphoid neoplasms (e.g. Hodgkin's disease, lymphoma, chronic lymphocytic leukaemia)
- Sarcoidosis
- Drugs (corticosteroids, immunosuppressants)
- Age (newborns and elderly)
- Tuberculosis infection acquired within last eight weeks
- Other conditions causing cell-mediated immune suppression
- Local skin damage (dermatitis, trauma, surgery)
- Incorrect handling and storage of tuberculin
- Poor technique (related to intradermal injection or measuring induration)

B. Factors that may increase skin reaction or give false positive reactions

- Exposure to or infection with nontuberculous mycobacteria
- Past BCG vaccination
- Trauma and irritation to site of intradermal injection before reading
- Poor technique

BCG Bacillus Calmette-Guérin vaccination

Box 2

Criteria for defining a tuberculin skin testing reaction as positive *

≥5 mm – in people with recent exposure (within 2 years) to tuberculosis + high risk for progression to active disease (e.g. <5 years of age, HIV infection, other immunosuppressive illness; see Table 1)

≥10 mm – in people with recent exposure to tuberculosis, regardless of BCG vaccination status; all non-BCG vaccinated people except for those with both low lifetime risk for tuberculosis infection and residence in geographical areas where exposure to environmental nontuberculous mycobacteriosis is common

≥15 mm – in all people regardless of BCG vaccination status

* This refers to the induration produced by an intradermal injection of purified protein derivative (PPD) equivalent to 5 units of PPD-S. These criteria are meant as suggestions only. Local tuberculosis control units should be consulted for local guidelines.

BCG Bacillus Calmette-Guérin vaccination

As skin test reactivity can wane with time, two-step skin testing is sometimes used. If the initial skin test is not positive, it can be repeated within one or two weeks (to minimise the possibility of new tuberculosis infection influencing the re-test result) when antigen from the first test would have stimulated recruitment of memory T cells to the area. This will also boost non-specific reactivity from BCG and nontuberculous mycobacteriosis. It is used either to detect infections from the distant past, for example in older people being screened before starting immunosuppressive therapy, or to establish a baseline when repeat testing is planned to monitor for new tuberculosis infection.

Interferon gamma release assays

The non-specificity of tuberculin skin testing (Box 1) and the dependence on well-trained staff to minimise human error are overcome by interferon gamma release assays. These laboratory tests are much more specific than tuberculin skin testing[3–6] because the antigens used are expressed by *M. tuberculosis*, but not BCG or most nontuberculous mycobacteriosis (exceptions include *M. kansasii, M. marinum, M. szulgai* and *M. flavescens*). The current blood tests either measure the amount of interferon gamma released by lymphocytes or quantify the number of T lymphocytes releasing interferon, after incubation with *M. tuberculosis* antigens.

Interferon gamma release assays are at least as sensitive as tuberculin skin testing for detecting recently acquired latent tuberculosis infections and may be even more sensitive for detecting recently acquired active infections.[5] Their increased specificity makes them useful in screening for recent tuberculosis infection in populations with a low incidence of tuberculosis and high uptake of the BCG vaccination. However, many studies show that tuberculin skin testing and interferon gamma release assays perform similarly in non-BCG vaccinated people at high risk for recent tuberculosis infection, if an appropriate cut-off (for example 10 mm induration) is used for tuberculin skin testing.[5]

It is not known if interferon gamma release assays are as sensitive as tuberculin skin testing for detecting remotely acquired (more than 5–10 years earlier) latent infections which may reactivate during immunosuppressive therapy. It is also suggested that interferon gamma release assays may be inferior to tuberculin skin testing in young children, particularly those under two years.[3]

Tuberculin skin testing does not require access to laboratory or phlebotomy so it is useful in remote settings and for infants and children. With well-trained staff, skin testing can be combined with counselling, education and clinical assessment for active tuberculosis. The distribution of tuberculin skin testing reactions in various populations[1,2] is better understood than that of interferon gamma release assays. Performance of interferon gamma release assays has not been tested in geographical areas where subclinical infections due to nontuberculous mycobacteriosis such as *M. marinum* or *M. leprae* are common.

Histopathology

Pathological examination of biopsied tissue may support a diagnosis of tuberculosis when bacteriology is negative or cannot be done, however histology is non-specific. Always ensure enough tissue is available for culture if it is required.

The patient's risk of tuberculosis should be considered to avoid misclassifying non-caseating granulomatous processes due to tuberculosis as sarcoidosis, Crohn's disease, or other granulomatous disease. Similarly, caseating granulomas due to tuberculosis in cervical lymph nodes of young children may be misclassified as nontuberculous mycobacterial lymphadenitis.

Approach to diagnosis

The key to early diagnosis of tuberculosis is to consider the possibility that a patient may be infected.

Active tuberculosis

If active infection is suspected in an adult, sputum samples should be analysed for mycobacteria unless the chest X-ray is normal and there are no respiratory symptoms. Even if non-pulmonary tuberculosis is suspected, it is important to realise that patients may also have pulmonary tuberculosis which is responsible for transmission of tuberculosis. Other testing (including further medical imaging, immunological tests or bronchoscopy) can then be carried out in consultation with a specialist.

Children rarely present with infectious tuberculosis and often have smear- and culture-negative tuberculosis even with severe forms of tuberculosis such as meningitis or miliary disease. Thus, early referral to a paediatrician or tuberculosis service is required in a child at high risk who is failing to thrive or is lethargic and listless.

Latent infection

Screening for latent tuberculosis is best carried out by clinicians who can exclude active tuberculosis and manage latent tuberculosis. The choice of tuberculin skin testing or an interferon gamma release assay will depend on local availability. Clinicians who are experienced in interpreting tuberculin tests and involved in population screening are likely to use tuberculin skin testing as the preferred test, using interferon gamma release assays when required for specificity.

Tuberculin skin test readings are interpreted after considering the clinical and epidemiological setting rather than defining a specific positive or negative cut-off. Skin testing by trained staff is done in conjunction with patient education, counselling, and screening for symptoms of tuberculosis.

Interferon gamma release assays will be preferred by clinicians assessing individual patients within a diverse practice. There is no need to refer the patient, as with the specialist tuberculin skin test. The result will be reported as positive, negative or indeterminate and not require integration of further epidemiological or clinical information.

As interferon gamma release assays are more specific, they are superior to tuberculin skin testing in people with a low lifetime risk for tuberculosis or with previous BCG vaccination. With trained staff, tuberculin skin testing lends itself to community screening and in populations at high risk for tuberculosis and it may be more sensitive for detecting remote (rather than recent) tuberculosis infections.

The best approach may integrate both tests and requires further study.* Whatever approach is used to diagnose infection, it is important to exclude active tuberculosis before considering the infection latent and offering preventive treatment.

Conclusion

It is clear that tuberculosis remains a major cause of disease globally, and many immigrants to Australia come from countries where tuberculosis is prevalent. It is therefore important for clinicians to maintain an appropriate index of suspicion about this disease.

Early diagnosis and effective management of active tuberculosis remain the most effective strategies for public health control of tuberculosis. As pulmonary tuberculosis is infectious, it is particularly important to consider the possibility of tuberculosis in patients with subacute and chronic infectious syndromes and with a cough for longer than two to three weeks. If such a patient has an abnormal chest X-ray, analysis of three morning sputum specimens will rapidly detect those with active transmissible infection. Tuberculin skin tests and interferon gamma release assays have no role in the initial investigation for active pulmonary tuberculosis. They are mainly used for detecting latent tuberculosis in people when active tuberculosis has been excluded, and for whom preventive treatment would be considered.

* See proposed approach (Fig. 5) online with this article at www.australianprescriber.com/magazine/33/1/12/18

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

1. Sputum culture is the definitive investigation for diagnosing latent tuberculosis.
2. A negative tuberculin skin test rules out the possibility of active tuberculosis.

Guidelines for thromboembolism prophylaxis in hospitals

New Australian guidelines for preventing venous thromboembolism are now available.[1] These guidelines give evidence-based recommendations for adult patients including pregnant women. Drugs covered by the guidelines include the heparins[2], fondaparinux, danaparoid, rivaroxaban, dabigatran etexilate, aspirin and warfarin. Mechanical options such as graduated compression stockings are also considered.

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Safe use of radiographic contrast media

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Summary

Injection of iodinated radiographic contrast media is generally safe, however with increased use adverse events are more likely to occur. The most important adverse effects include hypersensitivity reactions, contrast-induced nephropathy and thyrotoxicosis. There is no protocol that will prevent non-IgE-mediated anaphylaxis. In patients with moderate renal dysfunction, adequate hydration and use of as little contrast media as practical is recommended. Contrast-induced nephropathy is often transient. Metformin has been associated with lactic acidosis in patients receiving contrast media. It should therefore be discontinued for 48 hours starting on the day of the contrast study. The use of alternative non-iodinated contrast agents, particularly in ultrasound and magnetic resonance, is also growing. Gadolinium magnetic resonance agents have been associated with nephrogenic fibrosing sclerosis in patients with renal dysfunction.

Key words: adverse effects, gadolinium, kidney failure, metformin.

(Aust Prescr 2010;33:19–22)

Introduction

Contrast media are widely used in imaging, usually with CT, MRI, X-ray and more recently with ultrasound. Iodinated contrast media are the most commonly used contrast agents and are helpful in differentiating between normal and pathological areas. Common indications for contrast media include inflammatory, infective or neoplastic conditions. However, intravenous contrast is only indicated when the contrast will add diagnostic value. In patients with impaired renal function, a non-contrast scan or an alternative imaging examination may provide sufficient diagnostic information.

Iodinated contrast media

Iodine-based agents are compounds of 2,4,6 tri-iodobenzoic acid. Intravascular administration of iodinated contrast media is followed by a rapid passage into the extracellular space, water shift into the circulating volume and then excretion predominantly via the kidneys. Iodinated contrast media are classified into non-ionic and ionic. These can have high osmolality (ionic monomers) or low osmolality (ionic dimers, non-ionic monomers e.g. iopromide, and non-ionic dimers). The osmolality, viscosity and iodine content of contrast media are closely interrelated. Adverse effects increase with higher osmolality. Iodine content is not an independent indicator of adverse events. The non-ionic dimers are preferred due to lower osmolality and less chemotoxicity. However they are more viscous than non-ionic monomers, and more expensive.

Non-ionic agents

Iopamidol is a widely used non-ionic monomer which has an osmolality twice that of plasma at a concentration of 300 mg iodine/mL. Iodixanol is a non-ionic dimer and at a concentration of 300 mg iodine/mL has an osmolality approaching that of plasma (290 mOsmol/kg). Due to its higher cost, it is used selectively for examinations where osmolality may affect the examination quality (for example, cardiac CT coronary angiography and lower limb angiography for severe ischaemia).

Ionic agents

Ionic contrast media are contraindicated for intrathecal use. Only iotroxate, which binds reversibly to plasma protein promoting biliary excretion, is approved for intravenous cholangiography in Australia.

Non-iodinated contrast media

These agents are predominantly used in ultrasound (microbubble preparations) and MRI. The MRI agents such as gadolinium are paramagnetic and shorten the T1 relaxation time. They are very occasionally used in digital subtraction angiography in individuals hypersensitive to iodinated radiographic contrast media. Higher volumes are required for adequate contrast resolution.

Carbon dioxide is also used for digital subtraction angiography when iodinated contrast is contraindicated. However, it has significant technical limitations. It must not be used for angiography above the diaphragm or when there is a right-to-left shunt, to avoid cerebral ischaemic events from the bubbles.

Safety

Although contrast media are generally safe, adverse reactions do sometimes occur.

Hypersensitivity reactions

Hypersensitivity reactions to contrast media include both IgE and non-IgE-mediated anaphylaxis, with activation of mast cells, coagulation, kinin and complement mechanisms, inhibition of enzymes and platelet aggregation.[1]

Mild contrast media reactions with low osmolar media occur in less than 3% of patients and consist of skin rashes, nausea, flushing or urticaria. Moderate and severe hypersensitivity reactions include bronchospasm and wheezing, angioedema, coronary artery spasm, hypotension, cardiac arrhythmia, cardiac failure and loss of consciousness. Severe contrast reactions are uncommon, occurring in less than 0.04% of non-ionic iodinated contrast injections. Mortality due to contrast media reactions is low (less than one death per 100 000 patients).[2,3]

In the elderly, the mortality related to contrast media administration is significantly higher. Children are more sensitive to fluid volume change related to contrast administration.

Even very small doses of iodinated contrast may cause a reaction. Test injections are not recommended. The reaction may occur immediately, however delayed reactions after an hour or sometimes up to a week can also occur. These reactions (2–5%) are not due to anaphylaxis but they are possibly T cell-mediated and may consist of a maculopapular rash, urticaria and angioedema. The osmolality is strongly related to contrast media reactions. Most severe non-fatal contrast media reactions can be prevented by using low-osmolar contrast media.

Risk factors

Previous reaction to contrast media is the most important risk factor and carries a 20–60% absolute risk during subsequent exposure. Asthma increases the risk significantly, particularly the risk of bronchospasm. Beta blockers have been associated with hypersensitivity and may worsen bronchospasm. A history of multiple allergies requiring treatment increases the risk of acute reaction to iodinated contrast three- to fivefold. Vasovagal reactions can also occur during contrast media infusion.

Treatment

If a reaction occurs, infusion of the contrast media should be ceased immediately. Although mild reactions are often self-limiting and resolve without specific treatment, reactions that begin during or immediately after the injection should always be treated as the symptoms may progress. Vasovagal reactions are treated with elevation of the lower limbs and 0.6 mg of atropine as indicated. Treat mild delayed hypersensitivity reactions with an oral antihistamine.

Reactions associated with bronchospasm and wheezing, laryngospasm and stridor or hypotension should be treated immediately with adrenaline, intravenous fluids and oxygen, in addition to antihistamines with or without hydrocortisone. Intubation may be required and supportive medications may be necessary for 2–3 days in severe cases. Intramuscular adrenaline (1:1000) is the mainstay of treatment for severe reactions and can be repeated every 5 minutes if required. The initial dose for adults is 0.25–0.5 mL for those weighing less than 50 kg and 0.5 mL for those weighing more than 50 kg. Corticosteroids are not useful in the initial management of non-IgE-mediated reactions, but are believed to prevent or reduce delayed symptoms. Most patients recover from their reactions without any long-term morbidity.[4] Patients who have experienced severe reactions should be advised to carry a MedicAlert card. Severe reactions should be reported to the Office of Medicines Safety Monitoring (www.tga.gov.au/adr/bluecard.htm).

Patients with recurrent reactions should not be given contrast media so other modalities should be considered for investigations. However, when iodinated intravascular contrast must be given, a different and preferably lower osmolar agent should be used and premedication with corticosteroids for 24–48 hours before the procedure is widely practised.

Contrast-induced nephropathy

In this condition, renal tubular artery vasoconstriction and altered glomerular haemodynamics due to an elevated plasma oncotic pressure are caused by the contrast media. In renal insufficiency, acetylcysteine (a vasodilator and antioxidant) and fenoldopam (a vasodilator) have been studied as preventative strategies without definitive positive results.[5]

Acute renal injury is unlikely in patients who are hydrated and have normal renal function receiving contrast media less than 4 mL/kg. In patients with mild renal impairment, hydration before injecting contrast media usually prevents worsening renal function.

Alternative investigations such as non-contrast MRI, ultrasound and carbon dioxide digital subtraction angiography should be considered in patients with moderate to severe renal impairment. Dimeric non-ionic contrast media do not have an advantage over monomeric contrast media with respect to contrast-induced nephropathy.[6]

Most hospital-based radiology practices now require measurement of serum creatinine and calculation of glomerular filtration rate (GFR) before injection of contrast media. This is because renal failure is a potential factor in hospital deaths and long-term mortality of older patients with

mild renal impairment.[7] If GFR is less than 60 mL/min/1.72m^2, caution is urged and patients should be adequately hydrated when iodinated contrast media or gadolinium are used.

Metformin

Metformin has been associated with several cases of renal failure and lactic acidosis in patients who have received contrast media. If contrast media causes renal failure, metformin, which is renally excreted, can reach toxic levels resulting in lactic acidosis. It is now recommended that metformin be discontinued at least 12 hours before the contrast investigation and not be resumed for a minimum of 36 hours after the procedure, and longer if the serum creatinine has not returned to baseline. Alternative methods of managing the patient's glucose levels may be required during this interval.

Reducing the risk

The most important factors in reducing contrast-induced nephropathy are:

- avoiding repeated high dose studies at short intervals
- adequate hydration by intravenous route if necessary
- using low-osmolar non-ionic contrast media
- using diluted contrast media at the lowest volume practicable
- avoiding concurrent use of drugs that may cause renal vasoconstriction (non-steroidal anti-inflammatory drugs).

In most cases, renal function returns to baseline without specific treatment. In severe cases treatment is the same as for patients with tubular necrosis from other causes.

Nephrogenic systemic fibrosis

Gadolinium-based agents are associated with nephrogenic systemic fibrosis in patients with depressed renal function.[8,9] Most of these cases have been in people receiving high doses of gadolinium for CT or digital subtraction angiography because of known hypersensitivity to iodinated contrast.

Patients with a GFR of less than 30 mL/min are considered to be at a high risk of nephrogenic systemic fibrosis and gadolinium should be avoided completely. The risk in patients with a GFR of more than 60 mL/min receiving low doses of gadolinium (0.1 mL/kg) is negligible. The need for gadolinium studies in patients with mild renal impairment should be decided on clinical grounds.

Iodinated contrast media and the thyroid

Iodinated contrast-induced thyrotoxicosis is rare. Iodine does not have a significant effect on patients with normal thyroid function. Patients with Graves' disease and multinodular goitre are at increased risk, and those with thyrotoxicosis should not receive the contrast.

Patients with hyperthyroidism may develop a thyroid crisis and the accuracy of thyroid function tests will be affected by intravascular contrast media. These contrast media can also affect diagnostic thyroid isotope studies for up to eight weeks. Patients with thyroid carcinoma scheduled for treatment with radioactive iodine should not receive the contrast, as it may delay treatment for eight weeks.

Contrast media extravasation

New CT angiographic techniques involve contrast media power injectors, larger volumes and higher injection rates. As a result there is a slightly higher incidence of contrast media extravasation at or near the injection site. In severe cases, there is a risk of skin loss although this is less with the low osmolar agents.

Treatment is aimed at reducing skin metabolic needs with a cold pack for 20 minutes, and increasing the absorption of the contrast media with elevation and a crepe bandage.

Conclusion

Iodinated contrast media are commonly used during imaging with various diagnostic modalities. The low osmolar, non-ionic monomer contrast agents have a very low risk of serious reactions. Patients should be carefully evaluated for risk factors, including any history of previous reactions to contrast media, asthma, concurrent medical conditions with particular emphasis on renal and thyroid function, and current medications particularly metformin and beta blockers. Severe hypersensitivity reactions must be treated promptly like any other anaphylactic reactions with intramuscular adrenaline.

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Conflict of interest: none declared

There is a Comment for consumers online with this article at www.australianprescriber.com/magazine/33/1/19/22

Self-test questions

The following statements are either true or false (answers on page 27)

3. Reactions to contrast media may occur up to a week after the procedure.
4. Patients with renal impairment should not take metformin when receiving contrast media.

New drugs

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

Ambrisentan

Volibris (GlaxoSmithKline)

5 mg and 10 mg film-coated tablets

Approved indication: pulmonary arterial hypertension

Australian Medicines Handbook section 6.7

Pulmonary arterial hypertension may be idiopathic or be associated with other conditions such as connective tissue disease. The severity of pulmonary arterial hypertension is classified (I–IV) according to its effect on the patient's physical activity. Conventional treatment includes diuretics and warfarin, but more severe cases may need treatment with prostacyclins, such as epoprostenol, or endothelin receptor antagonists, such as bosentan and sitaxentan.

Ambrisentan is a selective antagonist of the endothelin type A receptor. This action blocks the vasoconstrictive effect of endothelin, a peptide produced by endothelial cells.

Like bosentan and sitaxentan, ambrisentan is taken orally. The tablets should not be chewed or crushed, but food does not affect bioavailability. Most of the dose is metabolised and excreted from the gut. The effective half-life is approximately nine hours. As the enzymes involved in the metabolism include cytochrome P450 3A4 and 2C19 there is a potential for drug interactions, but their clinical significance is currently unclear. Ambrisentan is not recommended for patients with liver disease, or if the patient has transaminase concentrations more than three times the upper limit of normal.

A dose-ranging study enrolled 64 patients with symptomatic pulmonary arterial hypertension despite conventional therapy. They could only walk an average of 343 metres in six minutes at the start of the study. After 12 weeks this had increased by approximately 36 metres irrespective of the dose. Pulmonary artery pressure decreased and there was less dyspnoea.[1]

Ambrisentan was then compared with placebo in two trials which randomised 394 patients. At the start of the study these patients could only walk an average of 340–355 metres in six minutes. One study used 5 mg or 10 mg doses. After 12 weeks these doses had increased the distance the patients could walk by 31–51 metres more than placebo. The other trial tested 2.5 mg and 5 mg. These doses increased the distance covered in six minutes by 32–59 metres more than placebo. A group of 280 patients completed an extension of the studies. After 48 weeks of taking ambrisentan they were able to walk 39 metres further than they were able to at the start of the studies.[2]

Ambrisentan's adverse effects and interactions will become clearer with more widespread use. The most frequent adverse effects in the trials, occurring more often than with placebo, were peripheral oedema, nasal congestion, sinusitis, flushing and palpitations.[2] Fluid retention may present as decompensated heart failure. Hepatic function must be monitored at least once a month because of the risk of liver damage. Haemoglobin should also be measured regularly as anaemia can occur in 7% of patients. Ambrisentan is contraindicated in pregnancy.

Although ambrisentan is the seventh drug to be approved for pulmonary arterial hypertension in recent years, the clinical benefit of these drugs is unclear. While they improve the six-minute walk test, this is a surrogate outcome. Their effect on survival is uncertain. There is also a need to compare the effectiveness of these drugs in longer-term studies.

☒ manufacturer did not respond to request for data

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Golimumab

Simponi (Schering-Plough)

prefilled syringe or autoinjector containing 50 mg in 0.5 mL

Approved indications: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

Australian Medicines Handbook section 15.2.1

Treatment with tumour necrosis factor inhibitors improves the signs and symptoms of severe autoimmune inflammatory joint diseases. Golimumab is a recombinant human monoclonal antibody that binds to tumour necrosis factor alpha, blocking its activity. It has been approved for several indications in Australia including:

- rheumatoid arthritis, in combination with methotrexate when other treatments have failed
- psoriatic arthritis, alone or in combination with methotrexate when other treatments have failed
- ankylosing spondylitis in adults.

Following subcutaneous injection, maximum serum concentrations of golimumab are reached within two to six days. Steady-state serum concentrations are reached after 12 weeks following monthly injections of golimumab 50 mg. The mean terminal half-life ranges from 11 to 14 days. The clearance of golimumab is increased in patients with anti-golimumab antibodies, but it is unclear what effect these antibodies have on safety and efficacy. Treatment with concurrent methotrexate reduces the number of patients who develop antibodies.

The efficacy of golimumab for moderate to severe active rheumatoid arthritis has been shown in three placebo-controlled trials totalling 1542 patients.[1–3] Patients in the trials had at least four swollen or tender joints. Golimumab 50 mg or 100 mg, or placebo, was given subcutaneously with or without methotrexate every four weeks. Response to treatment was measured according to the American College of Rheumatology 20% improvement (ACR20) or 50% improvement (ACR50) criteria. These are composite outcomes that assess the number of swollen and tender joints, the erythrocyte sedimentation rate or C-reactive protein concentration and global assessments of arthritis activity by the patient and doctor.

In the GO-FORWARD trial (444 patients), over half of the patients receiving golimumab plus methotrexate (55.1% with 50 mg and 56.2% with 100 mg) had a 20% improvement in symptoms by week 14, versus only a third receiving placebo plus methotrexate. Patients receiving golimumab with methotrexate also reported improvements in their physical function after 24 weeks. There were 12 serious infections during the trial – 11/311 patients receiving golimumab and 1/133 patients receiving placebo. One of the patients who had received two doses of golimumab 100 mg died from sepsis after developing pneumonia. None of the 92 patients who were being treated for latent tuberculosis (usually isoniazid) at baseline developed active infection during the trial. Three patients receiving the study drug had malignancies – these were squamous cell cancer, basal cell cancer and breast cancer.[1]

The GO-AFTER trial enrolled 461 patients who had previously used tumour necrosis factor inhibitors. They were allowed to continue methotrexate, sulfasalazine or hydroxychloroquine. After 14 weeks, significantly more patients had responded to golimumab than to placebo (ACR20: 35% with 50 mg and 38% with 100 mg vs 18% with placebo). Two patients receiving the study drug developed cancer – one was squamous cell carcinoma and the other was lymphoma. There were six serious infections with golimumab (pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection, urosepsis).[2]

In the GO-BEFORE trial, which enrolled 637 patients who had not previously received methotrexate, the primary end point was not met. However, in a post hoc modified intention-to-treat analysis, more patients receiving golimumab plus methotrexate had a 50% improvement in their symptoms by week 24, compared to those receiving placebo plus methotrexate (ACR50: 40.5% with 50 mg and 36.5% with 100 mg vs 29.4% with placebo). Unexpectedly, only the response rate to the lower golimumab dose was significantly better than placebo. The response of patients who received golimumab alone without methotrexate was not that different to those given placebo plus methotrexate (ACR50: 33.1% vs 29.4%).[3]

Nausea was the most common adverse event with golimumab plus methotrexate (13.9–15.1% vs 10% with

placebo and methotrexate). Other frequent events included elevated aspartate aminotransferase, elevated alanine aminotransferase, upper respiratory tract infection, dyspepsia and headache. There were two deaths in the trial – both patients were receiving golimumab. One death was from suicide, the other from cardiorespiratory arrest after surgery for a gluteal abscess. Two of the four malignancies that occurred in the trial were in patients receiving golimumab (breast cancer, Hodgkin's lymphoma). A patient receiving the higher golimumab dose was diagnosed with spinal tuberculosis (requiring surgery) eight weeks into the trial.[3]

Golimumab has also been assessed in patients with active psoriatic arthritis (three or more swollen or tender joints) in the GO-REVEAL trial. This study enrolled patients who had not previously received tumour necrosis factor inhibitors. Patients were allowed to continue methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids but were randomised to add injections of placebo (113 patients), golimumab 50 mg (146 patients) or golimumab 100 mg (146 patients) every four weeks. After 14 weeks, significantly more patients responded to golimumab than placebo (ACR20: 51% with 50 mg and 45% with 100 mg vs 9% with placebo). Patients receiving golimumab also had improvements in physical functioning and psoriasis symptoms (skin and nails). These benefits were irrespective of methotrexate use.

In the GO-REVEAL trial, upper respiratory tract infections and nasopharyngitis were the most commonly reported adverse events with golimumab and occurred more frequently than with placebo (10% and 10% with golimumab vs 6% and 4% with placebo). Elevated aspartate aminotransferase and alanine aminotransferase also occurred more frequently than with placebo. Alanine aminotransferase was increased in 24% of patients with golimumab 50 mg, 35% with golimumab 100 mg and 18% with placebo. Three malignancies were reported in the trial. These were in patients receiving the higher golimumab dose and included two cases of basal cell carcinoma and one case of prostate cancer. Other cancers were reported after the study period in patients who had received golimumab. These included small cell lung cancer (two cases), colon cancer, and basal cell carcinoma (two cases). A case of liver histoplasmosis was also reported in a patient who received golimumab.[4]

Golimumab has also shown benefit in people with ankylosing spondylitis (GO-RAISE trial). (Concurrent treatment with methotrexate, sulfasalazine, hydroxychloroquine, corticosteroids and NSAIDs was allowed during the trial.) Of the 356 adults enrolled in the study, significantly more people randomised to monthly golimumab had a 20% improvement in their symptoms compared to those in the placebo group (59.4% with 50 mg and 60% with 100 mg vs 21.8%) after 14 weeks. Patients in the golimumab group also reported significant improvements in back pain, morning stiffness and pain at night, but not in range of motion. There were more infections with golimumab than placebo. Similarly, fatigue, headache, diarrhoea, injection-site erythema and elevated aspartate aminotransferase and alanine aminotransferase concentrations were more common with the study drug than with placebo. One patient on the lower dose of golimumab had a myocardial infarction despite normal cardiac assessment at baseline.[5]

As golimumab affects the immune system there is a risk of serious infection, particularly in the elderly. Patients with active tuberculosis or other severe or opportunistic infections should not be given golimumab. If a patient tests positive for latent tuberculosis, they should be referred to a specialist for appropriate treatment before starting golimumab. It is important to monitor patients for infections while they are receiving golimumab. As the drug takes up to five months to clear from the body, patients should also be monitored after treatment has stopped. Patients should not be given live vaccines.

Golimumab has been associated with elevated liver enzymes so hepatic function should also be monitored during treatment.

Cancers, such as lymphoma, have occurred in patients given golimumab so caution is urged when prescribing this drug for patients who have a history of malignancy or develop a malignancy. Care should also be taken in patients with demyelinating disorders as golimumab can exacerbate these conditions.

Golimumab is contraindicated in moderate to severe heart failure. It should not be given with anakinra or abatacept. Some patients in the trials developed antinuclear antibodies following golimumab treatment, although none of them developed lupus-like symptoms.

A 50 mg dose of golimumab is recommended. It should be given subcutaneously once a month and patients may be able to do this themselves after training.

Golimumab was effective in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, and there seemed to be no advantage of the 100 mg dose over the 50 mg dose. Due to the lack of comparative trials, it is not known how it will compare to other tumour necrosis factor inhibitors currently used, although the fact that it can be self-administered once a month may be preferred by some patients.

☒ manufacturer declined to supply data

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Lacosamide

Vimpat (UCB Pharma)

50 mg, 100 mg, 150 mg and 200 mg tablets

Approved indication: partial seizures

Australian Medicines Handbook section 16.1.3

Many patients with epilepsy have partial seizures and these can become generalised. Carbamazepine or valproate are often used, but some patients require more than one drug to keep them free of seizures. Drugs which can be added on include gabapentin, lamotrigine, levetiracetam and now lacosamide.

The exact mechanism of action of lacosamide is uncertain. It is thought to stabilise neuronal membranes by enhancing the slow inactivation of voltage-gated sodium channels.

Oral doses of lacosamide are completely absorbed. Twice-daily doses produce steady-state concentrations after three days. Metabolism of the drug includes cytochrome P450 2C19, but 40% of the dose is excreted unchanged. As most of the drug and its metabolites are excreted in the urine, doses may need to be limited in patients with severe renal or liver impairment. The elimination half-life of lacosamide is approximately 13 hours.

The safety and efficacy of lacosamide was assessed in a trial which randomised 421 adults with simple or complex partial-onset seizures, with or without generalisation. These patients were having seizures despite having taken at least two anticonvulsants. They were randomised to add a placebo or lacosamide 200 mg, 400 mg or 600 mg daily. After dose titration, the patients were maintained on these doses for 12 weeks. The median reduction in seizure frequency was 39% with 400 mg and 40% with 600 mg. While lacosamide 200 mg reduced seizure frequency by 26% this was not significantly different from the 10% reduction in the placebo group.[1]

The 200 mg and 400 mg doses were studied in a similar placebo-controlled trial involving 485 adults. During 12 weeks of maintenance treatment, the median reduction in seizure frequency per 28 days was 35% with 200 mg and 36% with 400 mg daily. These reductions were significantly greater than the 21% reduction in the group who added placebo.[2] Another study of 421 patients also found a 21% reduction in the placebo group, while lacosamide 400 mg and 600 mg reduced seizure frequency by 37% and 38%.

The intravenous formulation of lacosamide can be used when patients are unable to take their tablets, for example because of surgery. As the tablets have very high bioavailability the intravenous dose is the same as the oral dose.[3]

In the clinical trials the most frequent adverse reactions were dizziness, altered vision, headache, nausea and vomiting. As the adverse effects were more frequent with lacosamide 600 mg, the maximum total daily dose for patients with normal renal function is 400 mg. There is also a dose-dependent prolongation of the PR interval on the ECG. Second or third degree heart block is therefore a contraindication to lacosamide.

The efficacy and safety of lacosamide in children and pregnant or lactating women is unknown. There was an increase in stillbirths in studies of pregnant animals.

While lacosamide adds to the choice of adjunctive anticonvulsants for partial seizures, not many patients became seizure free in the trials. Approximately 34% of patients taking lacosamide 200 mg daily will have a greater than 50% reduction in seizure frequency, but this is not always statistically different from placebo.[1,2] Some patients may have an increased number of seizures.[1] As the trials were relatively short for a chronic condition, there is a possibility that serious adverse reactions could emerge. One healthy volunteer developed hepatitis and nephritis after taking lacosamide. There may also be an increase in suicidal thoughts.

T manufacturer provided only the product information

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Prasugrel

Effient (Eli Lilly)

5 mg and 10 mg tablets

Approved indication: recurrent myocardial infarction

Australian Medicines Handbook section 7.2.2

Patients with myocardial infarction are at high risk of recurrence. Dual antiplatelet therapy, such as aspirin and clopidogrel, has been shown to reduce this risk.

Prasugrel, an adenosine diphosphate receptor antagonist of the thienopyridine class, is a new antiplatelet drug. It works by inhibiting platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ receptor on platelets. After oral administration, prasugrel is metabolised mainly by cytochrome P450 3A4 and 2B6. Its elimination half-life is 7.4 hours with the majority of the dose being excreted in the urine.

In a pharmacodynamic study of patients with acute coronary syndrome, prasugrel (60 mg loading dose, then 10 mg daily) was found to be a more potent inhibitor of platelet aggregation than clopidogrel (600 mg loading dose then 150 mg daily) in ex vivo blood tests.[1]

The approval of prasugrel is based on a comparative trial with clopidogrel in 13 608 patients. These people had acute coronary syndrome (10 074 with unstable angina or non-ST-elevation myocardial infarction and 3534 with ST-elevation myocardial infarction) and nearly all of them were undergoing percutaneous coronary intervention. Both prasugrel (60 mg loading dose then 10 mg daily) and clopidogrel (300 mg loading dose then 75 mg daily) were given in conjunction with aspirin (75–162 mg). The median duration of treatment was 14.5 months. The primary end point was a composite of cardiovascular death, non-fatal myocardial infarction or stroke. Significantly fewer patients receiving prasugrel had a cardiovascular event compared to those receiving clopidogrel (9.9% vs 12.1%). This was mostly due to the reduced incidence of myocardial infarction. Rates of stroke and death from cardiovascular causes not involving myocardial infarction were similar between groups. There were also significant reductions in the rates of stent thrombosis and urgent target-vessel revascularisation procedures with prasugrel. In the 3146 people with diabetes, less patients in the prasugrel group had a cardiovascular event than in the clopidogrel group (12.2% vs 17%).[2]

Obviously with antiplatelet drugs there is a risk of bleeding. The incidence of major haemorrhage in the trial was greater with prasugrel than with clopidogrel (2.4% vs 1.8%). This was fatal for 21 (0.4%) patients taking prasugrel and 5 (0.1%) patients taking clopidogrel. A post hoc analysis of harm versus benefit (based on bleeding and cardiovascular events) found that certain groups of patients did not benefit from prasugrel treatment. This included patients aged 75 or older and those weighing less than 60 kg. Prasugrel is not generally recommended for patients over 75 years but if the doctor decides it would benefit the patient, a lower maintenance dose (5 mg) is advised. Similarly, a lower maintenance dose is recommended if prasugrel is given to patients weighing less than 60 kg. Doctors should be aware that there is no evidence for the safety or efficacy of the lower dose of prasugrel. The post hoc analysis found that patients who had had a previous stroke or transient ischaemic attack had net harm and should not be given prasugrel.

Other adverse events included severe thrombocytopenia (0.3%), neutropenia (less than 0.1%) and colonic neoplasms (0.2%). Colonic cancers were reported twice as often with prasugrel than with clopidogrel, possibly because they were more likely to be detected due to the increased bleeding risk.[1]

Caution is urged when giving prasugrel to patients who have an increased risk of bleeding. This includes patients taking concomitant drugs, such as oral anticoagulants, non-steroidal anti-inflammatory drugs and fibrinolytics. Care should also be taken in patients who have had recent surgery, recurrent gastrointestinal bleeding or active peptic ulcers. To prevent bleeding complications, prasugrel should be stopped at least seven days before elective surgery. Premature discontinuation of prasugrel can increase the risk of thrombosis, myocardial infarction and death so in this situation patients should be monitored for cardiac events. It is contraindicated in patients with severe hepatic impairment.

Although prasugrel is metabolised by CYP3A4 it can be used concomitantly with other drugs metabolised by this pathway, such as the statins. It can also be given with digoxin, proton pump inhibitors and H_2 blockers. As prasugrel is a weak inhibitor of CYP2B6, a clinically significant effect may be seen when it is co-administered with drugs that are solely metabolised by CYP2B6 and have a narrow therapeutic window (such as cyclophosphamide or efavirenz).

When used with aspirin, prasugrel provides an alternative to other antiplatelet drugs for preventing atherothrombotic events in some patients with acute coronary syndrome who are undergoing percutaneous coronary intervention. However, there are only short-term clinical data for this drug (up to 15 months). Prasugrel appears to have more potent antiplatelet effects than clopidogrel so the risk of bleeding is higher.

T T manufacturer provided additional useful information

References †

1. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention. Circulation 2007;116:2923-32.
2. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.

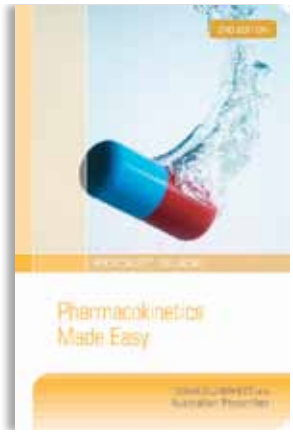
The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2009;32:80–1.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.emea.eu).

Erratum

The Medicines Line phone number is 1300 888 763.



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