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Editorial

Can pharmaceutical companies contribute to the quality use of medicines?

Peter R Mansfield, *Director, Healthy Skepticism Inc, and Visiting Research Fellow, University of Adelaide*

Key words: advertising, drug industry.

(Aust Prescr 2010;33:98–9)

Pharmaceutical companies can contribute to the quality use of medicines, when it is in their interests to do so. However, there are barriers against companies doing anything contrary to their interests. These include the Corporations Act, which requires officers to act in the interests of their company.[1] Consequently, the extent to which pharmaceutical companies can make a beneficial contribution depends on what they are rewarded for doing. This is determined largely by government policies.

Current government policies include granting patent monopoly protection and subsidies which enable companies to charge prices way above production costs, in the hope of providing an incentive for research and development. Unfortunately, this leads to companies being rewarded even if they distort research to maximise revenue rather than provide the reliable evidence base that is the essential foundation for the quality use of medicines. One example of this distortion is the use of multiple analyses of clinical trial data with selective reporting of favourable results.[2] Often such bias can only be detected if internal company documents are made available, for example by litigation.[2]

Paying high prices for new drugs is a less efficient way for taxpayers to fund research than direct grants to researchers. This is because most of the money from sales is diverted to other functions, especially promotion. Promotion involves synergistic combinations of many activities including persuasion disguised as education. Despite claims that some pharmaceutical sponsorship is 'unconditional', under the Corporations Act company officers 'may not be generous with company resources when there is no prospect of commercial advantage to the company'.[1] Sponsorship can influence medicines use indirectly by eliciting reciprocal obligations that can work in many ways, including making it seem rude to refuse to see the company's representatives or to criticise the company or its products.

Promotion can improve the use of medicines when the promoted drug is superior to the alternatives and the information provided is complete and accurate. However, according to *Australian Prescriber's* French equivalent (Prescrire International), between 2000 and 2009 only 2.0% of new drugs and new indications were a real advance.[3]

The current system provides frequent large rewards for misleading promotion, but only rare small punishments. During the past 25 years, I have not found a single drug advertisement that does not include misleading persuasion techniques. There is even less accountability for what sales representatives do behind closed doors. Sometimes entire sales teams are misled by their own companies.[2] Consequently, I believe the voluntary code of conduct for promotion is failing.

Health professionals are part of the problem because we often reward companies for producing misleading promotion by increasing use of the promoted drug. Many health professionals believe they can sort biased from unbiased information[4] but there is no proven method for preventing, diagnosing or

In this issue…

Vitamin D deficiency is a surprisingly common problem in Australia and often goes unnoticed. Devina Joshi and colleagues from Sydney discuss the controversial issue of sun exposure along with other risk factors, and give us a guide to diagnosing and treating vitamin D deficiency.

High blood pressure is also common in Australia. Mark Nelson tells us about the importance of individualising drug treatment, when needed, particularly in patients with comorbidities. He recommends which drug combinations to use and which to avoid.

Scheduling changes to codeine in May this year mean that higher doses of codeine are no longer available over the counter. Bridin Murnion reviews the evidence for the effectiveness of combination analgesics. She concludes that rescheduling of codeine is unlikely to significantly affect our analgesic options, but may reduce harms from overuse.

treating bias. Just as 19th century obstetricians, who did not understand the germ theory of disease, denied that they were asymptomatic carriers of the bacteria causing puerperal fever, many of today's health professionals deny their vulnerability to bias, because they do not know about the psychology of persuasion. Persuasion often works below the radar of conscious awareness. Overconfidence is a major risk factor for being misled.[4,5]

Another of the causes of problems in the pharmaceutical industry is that companies are currently allowed to perform, fund or influence multiple functions including manufacturing, research, promotion, education, regulation and policy development. Companies are rewarded for each function, not according to how it contributes to improving medicines use, but according to how effectively they use each function to increase sales revenue. There are therefore incentives for bias in the performance of each function.

I believe that the pharmaceutical industry's capacity to contribute to the quality use of medicines could be dramatically improved by reforms.[6] Splitting 'Big Pharma' into separate companies with one function each and abolishing patents and subsidies to allow free market competition between manufacturing companies would probably lead to prices for most worthwhile drugs plummeting below current co-payment prices.[7] The savings could be used to fund research and improvements in the use of medicines.[6] Such reforms could create an environment where pharmaceutical industry staff would be more consistently rewarded for contributing to the quality use of medicines. They would be empowered to use their considerable skills more consistently for the benefit of all.

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Note: The views expressed in this editorial are the author's and do not necessarily reflect the views of others in any of the organisations he is associated with.

Dr Mansfield holds a National Heath and Medical Research Council National Institute of Clinical Studies – Therapeutic Guidelines Ltd Fellowship.

Editorial

Can pharmaceutical companies contribute to the quality use of medicines?

Russell Edwards, *former Managing Director of Pharmacia and of Amgen Australia*

Key words: advertising, drug industry.

(Aust Prescr 2010;33:99–100)

Health professionals, accustomed to the sales and marketing activities of pharmaceutical companies, may not be aware that considerations about the quality use of medicines (QUM) are fundamental to the activities of the industry. Australia's three peak industry groups – the Australian Self Medication Industry, the Generic Medicines Industry Association and Medicines Australia – are partners in Australia's National Medicines Policy. QUM principles supporting judicious, safe, appropriate and efficacious use of medicines are embedded in the industry codes of conduct of Medicines Australia and the Australian Self Medication Industry. Industry groups and their member companies are increasingly applying QUM principles

in the development of educational and promotional activities. Individual companies are embracing QUM principles through internal staff training and the inclusion of QUM goals in the performance measures of key managers. One company has created a senior management position responsible for QUM. Medicines Australia includes a mandatory QUM training component in its continuing education program for medical representatives of member companies and for staff who have direct interaction with healthcare professionals or are involved in the review, development or approval of sales and marketing materials.

An important example of industry contribution to QUM is the production of consumer medicine information. This is based on the approved product information for prescription medicines.[1]

Twelve pharmaceutical companies have worked in partnership with the National Heart Foundation. Since its inception in 2003, the Heart Foundation Pharmaceutical Roundtable has conducted an extensive evaluation of the strengths and weaknesses of QUM in cardiovascular health, and selected a research project around an area of QUM which has strong potential to enhance cardiovascular health in both indigenous and non-indigenous Australians.[2] The adoption of this model of partnership to other therapeutic areas where QUM is important to health outcomes could further the contribution of industry to QUM.

Another example of industry contribution to QUM is the work entitled 'QUM from the start for health outcomes' developed by members of the Medicines Industry Liaison Group of the National Prescribing Service (NPS). It demonstrates the influence of QUM in all stages of drug development from discovery to commercialisation. This work shows that the application of QUM principles through the development process is important to the eventual product offering.[3]

The pharmaceutical industry is an important provider of information about its products and services to prescribers and consumers. It does this in a highly regulated environment which is designed to ensure safe, appropriate and well-informed use of medicines. However, the regulatory requirements of the Therapeutic Goods Administration and the QUM requirements in submissions to the Pharmaceutical Benefits Advisory Committee are also important drivers of adherence to QUM.

The management of the relationship between pharmaceutical companies and healthcare professionals or health consumer organisations is critical to achieving QUM. In Australia the Medicines Australia Code of Conduct is an example of a rigorous, enforceable framework for promoting ethical relationships between industry and healthcare professionals in an open and transparent way. The 16th edition of the Medicines Australia Code was authorised by the Australian Competition and Consumer Commission in December 2009. Enhancements to the Code should deliver public benefits through provisions such as protecting the public from exposure to inappropriate advertising and specifically regulating disease education and awareness campaigns. There are specific provisions and principles dealing with relationships between industry and health consumer organisations and there are specific enforcement mechanisms to deal with false and misleading conduct.

Pharmaceutical companies can unequivocally contribute to QUM. The challenge for industry is to increase its contribution to QUM. This challenge will succeed in companies in which QUM becomes part of organisational culture and QUM considerations feature in product development planning and corporate strategic planning. Effective contribution to QUM needs the strong support and endorsement of company leadership to manage the tension between commercial objectives and QUM. The industry will also be challenged to expand its contribution to a wider range of activities, partners and settings. Partnering on QUM issues with relevant organisations, including consumers, government and healthcare professionals, will also contribute to QUM and better health outcomes for patients.

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Note: The views in this editorial are the author's and do not necessarily reflect the views of others in any of the organisations he is associated with.

Mr Edwards is a consultant to Shire Pharmaceuticals, Independent Chair of the Medicines Australia Code of Conduct Monitoring Committee, and a shareholder of CSL. He has been a director of the Medicines Australia Board and is currently a director of the NPS Board.

Letters

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

Medicines Australia Code of Conduct

Editor, – I read with interest the article relating to Medicines Australia and the Committee regarding the monitoring of medications and code of conduct (Aust Prescr 2009;32:160–1). I agree the fines are enormous in terms of Australian standards although perhaps not necessarily so enormous in terms of the earning capacities of the various companies.

I would ask the following:

1. Who is involved in forming the Code of Conduct?
2. Who gets a copy of the Code of Conduct?
3. What happens to the money raised through these fines?
4. Who is represented on the Board of Medicines Australia?

David Bowman
Consultant Physician
Somerton Park, SA

Dr Brendan Shaw, Chief Executive, Medicines Australia, comments:

Dr Bowman should be assured that the 2010 edition of the Medicines Australia Code of Conduct carries appropriate sanctions. The maximum fine for a breach has increased from $200 000 to $300 000.

Importantly, however, non-monetary sanctions are often as strong a disincentive to a company as a fine. Having to send letters of retraction to doctors or take out corrective advertisements in the medical press can have an extremely negative impact on a company's reputation in the eyes of doctors, and serve as an effective deterrent.

Medicines Australia administers the Code of Conduct. An independent Code of Conduct Committee, chaired by a lawyer with extensive experience in trade practices law, adjudicates the complaints. The Committee consists of independent expert representatives of clinical, consumer and regulatory organisations. Details of the full Committee membership can be found on the website at www.medicinesaustralia.com.au/pages/page96.asp.

Medicines Australia reviews and updates the Code every three years to ensure it remains consistent with changing community standards. This is managed by an industry Code of Conduct Review Panel which seeks input from doctors and other healthcare professionals, professional associations, colleges, consumer organisations, patient groups and other groups or individuals who want to contribute.

The Code can be found on the Medicines Australia website at www.medicinesaustralia.com.au/pages/page251.asp. Hard copies are available free of charge to anyone upon request.

Revenue from fines raised through Code breaches covers the cost of administering the Code. Excess revenue is directed to a Special Purpose Fund which will be used to fund two initiatives aimed at improving outcomes in indigenous health.

The Board of Medicines Australia consists of an independent chairman and 12 managing directors of member companies, who are elected by the membership.

Nebivolol

Editor, – CSL Biotherapies is concerned by misrepresentation of data within the review of nebivolol hydrochloride in *Australian Prescriber* (2010;33:55–6). Several statements regarding nebivolol and its use in chronic heart failure are incorrect and do not accurately reflect current evidence.

The review states that the SENIORS trial 'was a *post hoc* analysis'. SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) was a randomised, double-blind, multicentre, international trial comparing nebivolol with placebo in elderly patients with heart failure on optimal standard therapy.[1] While there are several *post hoc* analyses that have stemmed from SENIORS, the efficacy results reported in the review pertain to the original SENIORS trial. It is inaccurate and misleading to state that SENIORS is a *post hoc* analysis as the results are outcomes of pre-specified end points in a study designed and powered to determine the effects of nebivolol on mortality and morbidity in this patient population.

The review stated that 'The target dose was reached by two-thirds of the patients in the nebivolol group and was associated with a significant reduction (relative risk reduction of 4.2%) in the composite end point of all-cause mortality or hospitalisation (due to a cardiovascular event), compared to placebo'. In SENIORS, there was a 14% relative risk reduction in the composite primary end point for nebivolol compared to placebo (hazard ratio=0.86, 95% CI 0.74–0.99, p=0.039).[1] The 4.2% reduction is the absolute, not relative, risk reduction, suggesting a number needed to treat of 24 patients for 21 months to avoid one event.[1]

The review's recommendation that 'until long-term data on its clinical use are available, it is probably better to continue to use the more established beta blockers' has the potential to mislead readers that 'more established' beta blockers have some benefit over nebivolol in heart failure. *Australian Prescriber* does not provide further information regarding these benefits or evidence to support this assertion. We are not aware of any head-to-head trials in elderly patients directly comparing the efficacy and safety of nebivolol to other beta blockers used for chronic heart failure.

SENIORS provides the best evidence to date of a treatment likely to be effective in elderly patients with a broad range of ventricular dysfunction.[1] Unlike previous beta blocker trials which excluded patients with left ventricular ejection fraction > 40%, SENIORS enrolled patients with preserved ejection fraction as well as systolic dysfunction.[1] SENIORS also enrolled patients who were older, with a mean age of 76 years, than those in previous beta blocker trials.[1] Thus, nebivolol is the only beta blocker to demonstrate proven efficacy in typical patients with chronic heart failure (aged 70 years and older with a wide range of left ventricular ejection fraction).

Nebivolol is currently approved for chronic heart failure in 72 countries worldwide (data held on file). In SENIORS the mean duration of follow-up was 21 months.[1] This is longer than the pivotal trials supporting the use of other beta blockers.[2–4]

We request that these inaccuracies regarding the efficacy of nebivolol for chronic heart failure are corrected, particularly given the potential for these errors to mislead readers.

Jane Leong

Medical Director

CSL Biotherapies

Melbourne

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The Editorial Executive Committee comments:

We agree that the results of the original SENIORS trial[1] should have been quoted rather than a *post hoc* analysis.[2] This has been corrected.[3] The confusion arose partly because there were four different articles published on the SENIORS trial. We asked CSL to provide a copy of the data supporting the approval of nebivolol by the Therapeutic Goods Administration, but only received the product information.

The SENIORS trial was randomised – patients were randomised to receive nebivolol 1.25 mg or placebo at the beginning of the trial. However, our original text was referring to the fact that patients were not randomised to receive different doses of nebivolol. For example, the dose was only increased to 2.5 mg or 5 mg in patients who tolerated the lower dose. Our original sentence has been deleted to avoid confusion.[3]

Regarding the efficacy of nebivolol, the relative risk reduction of 4.2% has been corrected to read the absolute risk reduction of 4.2%.[3]

The conclusion that it is probably better to continue to use the more established beta blockers until there are more long-term data for nebivolol remains the view of the Editorial Executive Committee. In our opinion, there are currently more robust data for beta blockers such as carvedilol, bisoprolol and metoprolol succinate than for nebivolol.[4]

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Vitamin D deficiency in adults

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Summary

Vitamin D deficiency is a common condition that affects a significant number of Australians. Vitamin D is important in the maintenance of bone health, and deficiency leads to osteomalacia and contributes to fragility fractures. Deficiency has also been implicated in a wide variety of extra-skeletal conditions. Vitamin D can be easily assessed in patients by measuring serum 25-hydroxyvitamin D. Replacement of vitamin D needs to be tailored for each patient and depends on the severity of the deficiency. Toxicity is unlikely with vitamin D when it is administered as cholecalciferol as it has a wide safety window. The adequacy of replacement should be monitored and in cases of persistently low concentrations, malabsorptive conditions (especially coeliac disease) should be excluded.

Key words: calcitriol, cholecalciferol, ergocalciferol.

(Aust Prescr 2010;33:103–6)

Introduction

Australia is well known for its abundance of sunshine. Hence, it is perhaps surprising that vitamin D deficiency is a common condition affecting a large proportion of Australians. A recognised consequence of low vitamin D is osteomalacia in adults.[1] It also contributes to osteoporosis, that is fragility fractures, in part through increased risk of falls.[2] Vitamin D deficiency has also been implicated in other conditions including cardiovascular disease, increased cancer risk and mortality, falls, sarcopenia, diabetes, multiple sclerosis, osteoarthritis, epilepsy and cognitive dysfunction.

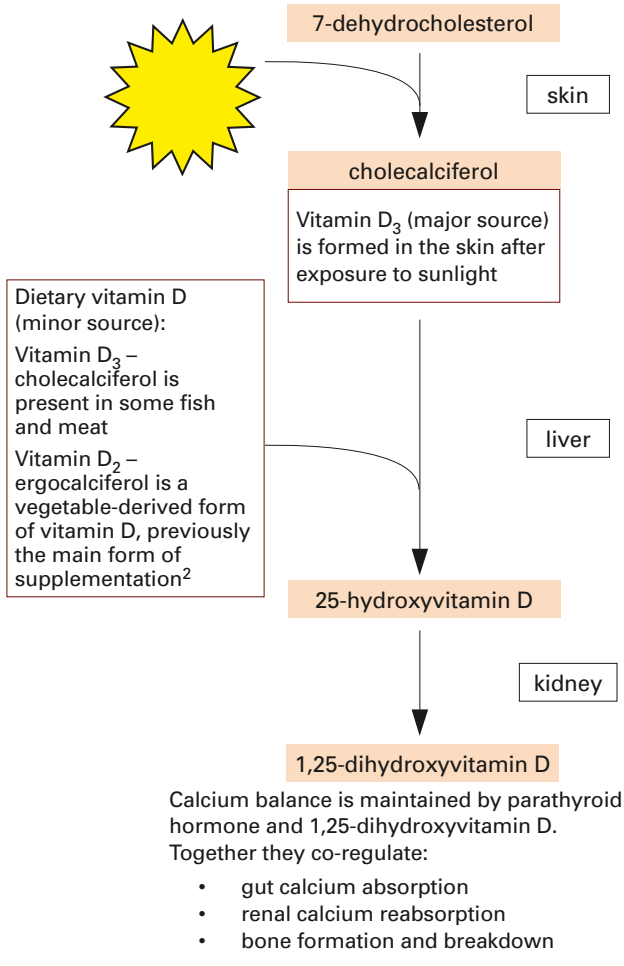
Metabolism and function of vitamin D

The two main forms are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) (see Fig. 1). These are transported to the liver and metabolised to 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2 which are the major circulating forms of vitamin D and are measured in most assays. A second hydroxylation takes place in the kidney to form 1,25-dihydroxyvitamin D_3, also known as calcitriol, and 1,25-dihydroxyvitamin D_2. These are the activated forms of vitamin D and have three main functions:

- enhancing absorption of calcium and phosphate from the small intestine
- inhibiting parathyroid hormone synthesis and secretion
- mineralising the bone matrix.[3]

Fig. 1

Vitamin D metabolism



Impaired renal function results in reduced production of 1,25-dihydroxyvitamin D, whereas hepatic function, even if it is severely impaired, does not seem to have a major effect on vitamin D metabolism.

Sources of vitamin D

The main source of vitamin D comes from exposure of the skin to sunlight. Hence there is considerable seasonal variation with concentrations higher at the end of summer compared to other seasons. Vitamin D_3 is found in fatty fish such as herring, salmon and mackerel. Other sources include eggs, meat and fortified foods such as margarine (Fig 1). For most Australians, adequate vitamin D is unlikely to be achieved through dietary sources alone without fortification.[4]

Controversies regarding sun exposure

Guidelines on sun exposure must be tempered by the high prevalence of skin cancers in this country. Much controversy has surrounded the topic of how much sunshine is enough and how much is too much. It is a subject where there has often been a lack of consensus among medical specialists themselves and this problem is further compounded in transferring this message to the public.[5]

Recommending sun exposure

Recommended exposure of 5–15 minutes of sunlight 4–6 times a week outside the hours of 10 am–2 pm seems prudent (Table 1).[1] Certainly, avoidance of the most dangerous ultraviolet exposure in the middle of the day is appropriate, especially in summer, with responsible use of ultraviolet blocking agents. Guidelines on exposure to sunshine need to be tailored to the individual – one size does **not** fit all. Many factors need to be considered including geographical location such as latitude, season, time of day, skin colour, age and particularly clothing.

Dermatologists have expressed concern about relaxation of sun protection messages, which have played a large role in the media campaigns to reduce the incidence of skin cancers. Important caveats include some knowledge by the public of the ultraviolet index* – concentrations above 3 require sun protection. People who are at the highest risk of skin cancers, such as those who are immunosuppressed, should take even more stringent precautions in the sun.[5] On the other hand, people with darker skin can require 3–4 times more sun to achieve the same vitamin D synthesis.[3]

* The ultraviolet index is an open-ended linear scale which rates the danger of solar ultraviolet radiation intensity on a daily basis. Each point on the scale is equivalent to 25 milliWatts/m^2 of ultraviolet radiation. A rating of 0–2 is low, 3–5 is medium, 6–7 is high, 8–10 is very high and 11+ is extreme.

Table 1

Recommendations of sun exposure for adequate vitamin D synthesis on exposed arms and legs (outside the hours of 10 am–2 pm) †

Region	Duration (minutes)	
	Summer	Winter
Cairns	6–7	9–12
Townsville	5–7	9–13
Brisbane	6–7	15–19
Sydney	6–8	26–28
Melbourne	6–8	32–52
Adelaide	5–7	25–38
Perth	5–6	20–28
Hobart	7–9	40–47

† Adapted from reference 3

Causes of vitamin D deficiency [3]

Reduced synthesis of cholecalciferol in the skin

Reduced sun exposure can result from ageing, veiling, illness or immobility (staying indoors). As people age, their ability to synthesise cholecalciferol from sun exposure decreases. Also, people with dark skin synthesise less cholecalciferol from sun exposure than do people with light skin.

Disorders of malabsorption

Small bowel disorders – especially coeliac disease and inflammatory bowel disease, infiltrative disorders (for example lymphoma, granuloma) and small bowel resection – can cause malabsorption of vitamin D. Other conditions such as pancreatic disorders (chronic pancreatitis, cystic fibrosis) or biliary obstruction (primary biliary cirrhosis) can have the same effect.

Enhanced degradation of 25-hydroxyvitamin D

Drugs such as rifampicin and anticonvulsants enhance the degradation of vitamin D which may contribute to or exacerbate vitamin D deficiency.

Groups at highest risk of vitamin D deficiency [6,7]

Older people in residential care or those who are hospitalised, particularly people with hip fractures, are at risk of vitamin D deficiency, as are people living in institutional facilities. This is partly explained by age-related thinning of the skin and partly due to reduced sunlight exposure. Other at-risk groups include dark-skinned women (especially if veiled), ethnic minorities (Asian, Middle-Eastern origin) and refugees. Patients with malabsorptive syndromes or who are obese also are at increased risk of vitamin D deficiency. Hyperparathyroidism increases the metabolism of vitamin D and thus decreases its

half-life. Supplementary requirements are therefore greater in patients with hyperparathyroidism.

Diagnosing vitamin D deficiency

Vitamin D deficiency is usually asymptomatic, but signs and symptoms can include muscle aches and particularly weakness (proximal limb girdle). It is often seen in older people with osteoporosis. While there is debate about the benefit of vitamin D supplementation in preventing osteoporotic fractures, there is evidence that it may reduce falls risk.[2] Also, virtually all of the currently approved osteoporosis treatments have been evaluated in the presence of adequate vitamin D concentrations so these should be achieved as part of the approach to osteoporosis treatment.

Vitamin D deficiency can be detected using the 25-hydroxyvitamin D radioimmunoassay. While there is debate as to ideal concentrations, the following could be used to guide a clinical approach:

- vitamin D sufficiency > 75 nmol/L
- sub-optimal levels 50–75 nmol/L
- vitamin D insufficiency 25–50 nmol/L
- vitamin D deficiency 15–25 nmol/L
- severe vitamin D deficiency < 15 nmol/L.

This assay should also be used to monitor therapy. Virtually all commercial assays now measure 25-hydroxyvitamin D_2 as well as 25-hydroxyvitamin D_3. Parathyroid hormone and ionised calcium should be measured as an adjunct to 25-hydroxyvitamin D. Parathyroid hormone is usually elevated in the context of vitamin D deficiency. The aim of treatment is to normalise 25-hydroxyvitamin D, parathyroid hormone and calcium.

Vitamin D supplementation

The lower the 25-hydroxyvitamin D serum concentration, the more aggressive replacement therapy regimen is required to achieve acceptable concentrations rapidly. The greatest benefits are seen in high-risk individuals with decreased bone mineral density. In a meta-analysis of randomised controlled trials, vitamin D and calcium reduce the risk of falls and hip and other non-vertebral fractures in older people.[8] However, the target range of 25-hydroxyvitamin D is still debated with values anywhere between 50 and 110 nmol/L being advocated. In patients treated with bisphosphonates, adequate calcium and vitamin D are required for efficacy of treatment. Many supplements only have 400 IU of vitamin D, but there is evidence that at least 800 IU is required for adequate benefit.

Benefits of vitamin D supplementation have also been reported in other conditions including diabetes and the metabolic syndrome,[9] neoplasia[10,11] and cognitive dysfunction.[12] Although most of these studies are preliminary, they indicate potential benefits that may be of great significance in the future.

Daily requirements

Daily requirements for vitamin D are around 800–1000 IU, but larger doses are needed for patients who are already deficient. For moderate deficiency, that is 15–25 nmol/L, oral supplementation with 3000–5000 IU daily for 6–12 weeks can be used to replete stores followed by a maintenance dose of 1000–2000 IU per day. Vitamin D status should be assessed 3–4 months after commencing treatment as vitamin D is stored in fat and muscle and there is a lag time before normalisation of serum concentrations.[3]

For severe vitamin D deficiency, that is 25-hydroxyvitamin D less than 15 nmol/L, the intramuscular form of cholecalciferol 100 000 IU (megadose therapy) may be more suitable to replenish stores more quickly and effectively.[3] This is especially pertinent for patients with malabsorption, acute medical illnesses and poor dietary compliance. Currently, such formulations are only available for specialists under a special access scheme.

Vitamin D in pregnancy

There is little consensus regarding the optimal dose of vitamin D required by pregnant women. The arbitrary addition of 400 IU vitamin D to most multivitamins sold for use during pregnancy is based on little evidence and is usually insufficient for most women who do not receive adequate sunshine or are dark-skinned or covered up. The pre-pregnancy 25-hydroxyvitamin D status is the best predictor of levels during pregnancy and hence the best gauge of requirements during pregnancy. Even supplements of 1000–1600 IU vitamin D have been found to be inadequate in many cases of deficiency. Supplementation with 2000–10 000 IU has usually resulted in acceptable concentrations without any adverse effects. Whether these observational studies can translate into widespread recommendations remains to be studied in large interventional studies.

The mother's vitamin D status is important because it will determine that of her infant – neonatal vitamin D concentrations correlate closely with those of the mother.[13]

Vitamin D supplements

Cholecalciferol (vitamin D_3) 1000 IU or 25 microgram is the supplement most commonly used and costs approximately 11–16 cents per capsule. It is not subsidised by the Pharmaceutical Benefits Scheme. Multivitamin supplements with 32–200 IU per tablet are not adequate to treat or prevent vitamin D deficiency.[3]

Calcitriol (1,25-dihydroxyvitamin D_3) is generally not suitable for treatment of vitamin D deficiency as it has a narrow therapeutic window resulting in an increased risk of hypercalcaemia or hypercalciuria. This is especially true in nursing home residents who often have quite severe vitamin D deficiency. Calcitriol has a role in the treatment of vitamin D deficiency in renal failure where there is inability to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Serum calcium concentrations and renal function must be monitored closely under these circumstances.

Adverse effects of treatment

Vitamin D toxicity can be caused by excess oral intake, but not by prolonged exposure to sunshine. No evidence of toxicity has been found in cholecalciferol doses up to 4000 IU daily. Even doses of 100 000 IU at more than three-monthly intervals have not been associated with toxicity. Vitamin D intoxication causes hypercalcaemia and can present with symptoms of anorexia, nausea, constipation and depression. Examination and investigations may demonstrate renal calculi, renal impairment and anaemia.

Conclusion

Vitamin D deficiency is common in Australia and contributes to significant morbidity. It is easily assessed by measuring serum 25-hydroxyvitamin D concentrations. Replacement needs to be tailored depending on the degree of insufficiency, and vitamin D concentrations should be monitored after 3–4 months. If vitamin D is low or proving difficult to replenish, ensure compliance and exclude malabsorption conditions such as coeliac disease.

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There is information for consumers on this article at www.australianprescriber.com

Self-test questions

The following statements are either true or false (answers on page 131)

1. Adequate vitamin D can be obtained from diet alone.
2. Calcitriol should be used for vitamin D replacement in people with normal renal function.

Dental notes

*Prepared by **Michael McCullough**, Chair, Therapeutics Committee, Australian Dental Association*

Vitamin D deficiency in adults

See article in this issue, p.103–6

Bone metabolism involves highly complex interactions of multiple factors, not the least of which is the patient's level of serum vitamin D. Skeletal bone health has become a topic of considerable interest to dentists over the last 5–6 years with the recognition of osteonecrosis of the jaw in patients taking bisphosphonates long term. Although this is an uncommon event – probably occurring after tooth extraction in 1/500 to 1/1500 patients on oral bisphosphonates for the prevention of osteoporosis[1] – the condition can be devastating with limited available effective treatment. Dental treatment must be undertaken with informed consent and there are good guidelines for this.[2] Vitamin D supplementation may play a part in the management of our patients' bone health, but dentists need to be aware that treatment of bone disease, and any changes in medication for bone health, should only be made in consultation with the treating physician and never on our recommendation alone.

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Combination analgesics in adults

See article in this issue, p.113–5

Most patients presenting to dentists with pain have some form of acute pain. This can usually, and predictably, be managed by removing the cause of the problem through a thorough diagnosis and effective dental treatment. However, some pain may remain for a short period of time after treatment. It is essential that dentists ascertain whether the patients have been taking analgesics or other medications to help manage their pain. The prescription of any analgesia after treatment should be done carefully to ensure minimisation of potential adverse effects, interactions and overdoses particularly in patients who have already been self-medicating to obtain pain relief. Some patients may use extra medications without the dentist's knowledge so all patients should be informed and educated about safe drug use and doses. If there is any doubt, patients should adhere to the dosage stated on the packet and take the drug in accordance with the manufacturer's instructions, unless the prescribing doctor advises otherwise.

Finding medicines information online

Following the closure of the Therapeutic Advice and Information Service (TAIS) on 1 July 2010, NPS has compiled a guide to medicines information resources on its website, which can be accessed via the health professional webpage. Please note that some of the listed resources are freely available and others need a subscription fee. The URL is www.nps.org.au/medicines_information_guide

Change of number for Medicines Line

As of 1 July 2010, the number for the NPS consumer telephone information service Medicines Line has changed to 1300 MEDICINE (1300 633 424). Medicines Line provides information to consumers about prescription, over-the-counter and complementary medicines. NPS is collaborating with healthdirect Australia to deliver Medicines Line and all calls are answered in the first instance by a registered nurse. Questions may be answered on the spot, or callers may be referred to their general practitioner, pharmacist or another health professional. Complex enquiries may be triaged to an NPS pharmacist.

New branding for NPS

NPS has launched a new 'look and feel' as of 1 July 2010. Rather than use the full reference to National Prescribing Service, we are using the NPS acronym which is how many people already refer to us. We have also introduced a new tagline – Better choices, better health. For more information and to view the new logo, visit www.nps.org.au

Drug treatment of elevated blood pressure

***Mark Nelson**, Professor and Chair, Discipline of General Practice Professorial Research Fellow, and Senior Member, Menzies Research Institute, University of Tasmania, Hobart*

Summary

The decision on when to start drugs for the treatment of elevated blood pressure should be determined by an individual's absolute risk of having an adverse cardiovascular event. The choice of drug depends on its safety and effectiveness and its indications and contraindications for individual patients. Most patients will require two or more drugs to reach their target blood pressure. The main classes of antihypertensive drugs are equally effective at reducing blood pressure, but beta blockers are no longer recommended as first-line treatment for most patients.

Key words: antihypertensives, cardiovascular disease, hypertension.

(Aust Prescr 2010;33:108–12)

Introduction

All patients with elevated blood pressure should be encouraged to have a healthy lifestyle.[1] Although there are benefits from weight loss, salt and alcohol reduction and exercise, these lifestyle changes may be insufficient to control a patient's blood pressure. This leaves them at risk of coronary heart disease, stroke and renal failure. If the high blood pressure is confirmed by accurate measurements on several occasions, drug treatment should be considered.

Who should receive drug therapy?

Drug treatment for elevated blood pressure should not be based solely on accurate blood pressure readings. It should also consider an individual's absolute cardiovascular risk – their risk of having a stroke or myocardial infarction over a specified period of time, usually five years.[2] An absolute risk calculator can be used to identify who is most likely to benefit from treatment.[3] The previous underestimation of risk in Aboriginal and Torres Strait Islander people by such calculators has been addressed in the recently published Australian risk calculator.[4–6]

Immediate treatment to lower blood pressure is recommended for patients with confirmed hypertension (multiple measures on at least two separate occasions):

- systolic blood pressure 180 mmHg or greater
- diastolic blood pressure 110 mmHg or greater
- systolic blood pressure 160 mmHg or greater and diastolic blood pressure 70 mmHg or less.

Patients with associated conditions (for example, stroke or myocardial infarction) or evidence of end-organ damage (for example, microalbuminuria, left ventricular hypertrophy) also need urgent treatment (Fig. 1).

Starting drug therapy

Once the decision has been made to start drug therapy, the choice of antihypertensive drug should be based on the patient's age and the presence of associated clinical conditions or end-organ damage. The presence of other diseases may favour or limit the use of particular drug classes and there may be potential interactions with other drugs (Table 1). Cost and the ease of adhering to treatment should also be considered. Antihypertensive drugs in different classes have similar efficacy. In uncomplicated cases the recommendation is to start with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor antagonist, calcium channel blocker or diuretic (in the aged).[2] Beta blockers are no longer recommended as first-line treatment for uncomplicated high blood pressure as meta-analyses show they have an adverse relative risk of stroke and new onset diabetes compared to other drugs.[7,8]

Target blood pressure

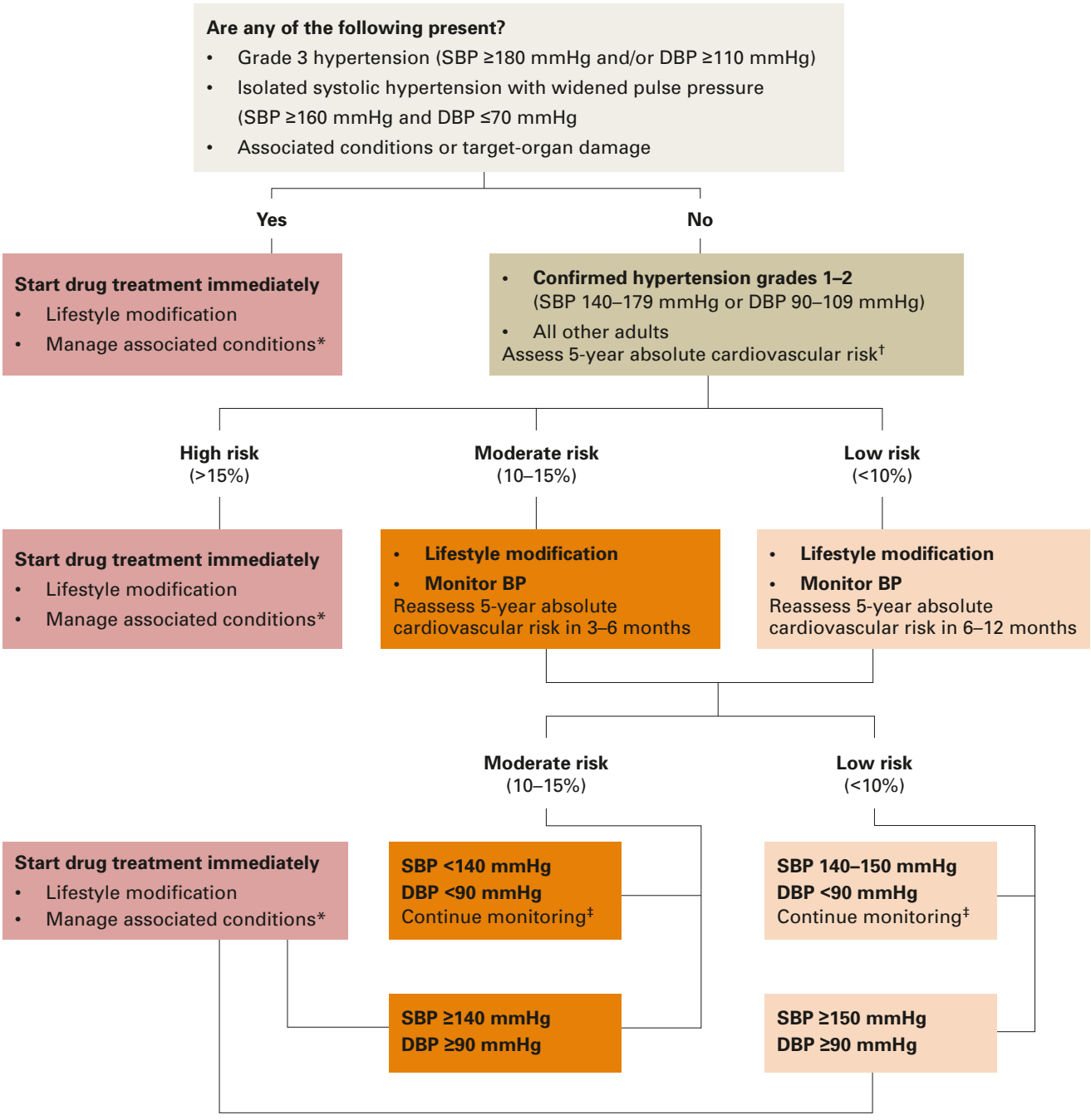
A patient's comorbidity helps to determine which blood pressure to aim for. In uncomplicated hypertension the target should be 140/90 mmHg or lower if tolerated. The target is under 130/80 mmHg in patients with end-organ damage or conditions such as diabetes, and under 125/75 mmHg in patients with proteinuria (>1 g/day).

It is important that patients be treated to reach their recommended blood pressure. Failure to do so leaves patients at significant residual adverse risk.

Start with the lowest recommended dose of the selected drug and review the patient after six weeks. If the drug is not well tolerated or is ineffective, change to a drug of a different class. If the target blood pressure is still not reached, add a further drug from a different pharmacological class at a low dose, rather than increasing to the maximum dose of the first drug.

Fig. 1

When to start drug treatment for hypertension [2]



BP blood pressure SBP systolic blood pressure DBP diastolic blood pressure

* For example, diabetes (strict glycaemic control lowers cardiovascular risk), lipid disorders (cholesterol-lowering therapy reduces the risk of primary and secondary coronary events). See National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Position statement on lipid management 2005 (www.heartfoundation.org.au).

† For Aboriginal and Torres Strait Islander adults, consider managing as though at a higher risk level

‡ Continue lifestyle modification, monitor blood pressure and reassess absolute cardiovascular risk regularly. Note that patients with mild hypertension will require antihypertensive drug treatment if their absolute risk of cardiovascular disease is elevated due to changes in other risk factors.

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Table 1

Choice of antihypertensive drug in patients with comorbid and associated conditions [2]

Condition	Potentially beneficial	Potentially harmful	
		Caution	Contraindicated
Angina	Beta blockers (except oxprenolol, pindolol), calcium channel blockers, ACE inhibitors		
Atrial fibrillation	Remodelling: ACE inhibitors, angiotensin receptor antagonists* Rate control: verapamil, diltiazem, beta blockers		
Asthma/COPD		Cardioselective beta blockers (e.g. atenolol, metoprolol): use cautiously in mild–moderate asthma/COPD only	Beta blockers (except cardioselective drugs)
Bradycardia, second- or third-degree atrioventricular block			Beta blockers, verapamil, diltiazem
Depression		Beta blockers, clonidine, methyldopa, moxonidine	
Gout	Losartan	Thiazide diuretics	
Heart failure	ACE inhibitors, angiotensin receptor antagonists,* thiazide diuretics, beta blockers† (bisoprolol, carvedilol, metoprolol controlled release), spironolactone	Calcium channel blockers (especially verapamil, diltiazem)	Alpha blockers in aortic stenosis Beta blockers in uncontrolled heart failure
Post myocardial infarction	Beta blockers (except oxprenolol, pindolol), ACE inhibitors, eplerenone		
Pregnancy§			ACE inhibitors, angiotensin receptor antagonists, diuretics, calcium channel blockers (before 22 weeks gestation), atenolol
Chronic kidney disease	ACE inhibitors, angiotensin receptor antagonists*		
Tight bilateral renal artery stenosis (unilateral in patient with solitary kidney)		ACE inhibitors, angiotensin receptor antagonists	
Post stroke	ACE inhibitors, angiotensin receptor antagonists, low-dose thiazide-like diuretics		
Type 1 or type 2 diabetes with proteinuria or microalbuminuria	ACE inhibitors, angiotensin receptor antagonists*	Beta blockers, thiazide diuretics‡	

ACE angiotensin-converting enzyme COPD chronic obstructive pulmonary disease

* Careful monitoring of kidney function is required if a combination of ACE inhibitors and angiotensin receptor antagonists is used

† Particular beta blockers are now indicated in the treatment of heart failure. See the Heart Foundation Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006 (available at www.heartfoundation.org.au).

‡ When used in combination with an ACE inhibitor, may be beneficial in type 2 diabetes

§ Currently under review by the Heart Foundation

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This treatment approach maximises efficacy while minimising adverse effects. Titrate the dose of one drug then the other until the target blood pressure is reached. Additional drugs may be required.

Attaining and maintaining the target blood pressure may be assisted by:

- choice of long-acting drugs to provide once-daily administration
- regular assessment and encouragement of drug adherence
- treating the patient as a partner in management decisions and involving the patient's family when appropriate
- providing specific written instructions and patient education materials
- discussing the use of dose administration aids (e.g. dosette boxes, blister packs) and home medicines review
- use of self-measurement of blood pressure for monitoring, if appropriate
- evaluating the social and economic barriers that may affect medication supply and storage
- using effective combinations (Table 2) when more than one drug is required.

Combination therapy

Approximately 60% of patients with elevated blood pressure will not achieve their blood pressure targets with monotherapy. Most patients will require a combination of two or more drugs to achieve adequate blood pressure control. There are several effective combinations (Table 2). In the ACCOMPLISH trial an ACE inhibitor and calcium channel blocker combination reduced cardiovascular events more than a combination of the ACE inhibitor with a diuretic.[9]

Long-term drug treatment

Drug treatment is usually lifelong, as age is the most important determinant of adverse risk, unless the blood pressure is well controlled by profound lifestyle changes.[10] If blood pressure is normal and stable, the interval between visits can be lengthened, for example, review every three months for the next 12 months and six-monthly thereafter.

If treatment is stopped, the patient's blood pressure should be checked regularly. Patients should continue the lifestyle changes and agree to resume drug treatment if their blood pressure rises again.

Resistant blood pressure

Failure to control blood pressure can be due to a wide range of prescriber, patient, healthcare system and drug related factors. If blood pressure remains above the target despite maximal doses of at least two appropriate drugs after a reasonable period, consider the following potential explanations:

- non-adherence to drug therapy and lifestyle modifications
- secondary hypertension (e.g. sleep apnoea, chronic kidney disease)

Table 2

Recommended and discouraged drug combinations for hypertension [2]

Recommended combinations			**Recommendation**
ACE inhibitor or angiotensin receptor antagonist	plus	calcium channel blocker	Diabetes or dyslipidaemia
	plus	thiazide diuretic	Heart failure or post stroke
	plus	beta blocker	Post myocardial infarction or heart failure
Beta blocker	plus	dihydropyridine calcium channel blocker	Coronary heart disease
Thiazide diuretic	plus	calcium channel blocker	
	plus	beta blocker	**Not** with glucose intolerance, metabolic syndrome or diabetes
Combinations to avoid			**Recommendation**
ACE inhibitor or angiotensin receptor antagonist	plus	potassium-sparing diuretic	Avoid because of risk of hyperkalaemia
Verapamil	plus	beta blocker	Avoid because of risk of heart block
ACE inhibitor	plus	angiotensin receptor antagonist	In a large trial, combination therapy did not reduce cardiovascular death or morbidity in patients with vascular disease or diabetes while increasing the risk of hypotensive symptoms, syncope and renal dysfunction

ACE angiotensin-converting enzyme

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- use of drugs that may increase blood pressure (e.g. non-steroidal anti-inflammatory drugs, prednisolone)
- alcohol or recreational drug use
- high salt intake (particularly in patients taking ACE inhibitors or angiotensin II receptor antagonists)
- 'white coat' hypertension
- blood pressure measurement artefact
- volume overload (especially with chronic kidney disease).

Drug treatment in older people

In the elderly, isolated elevated systolic blood pressure is more prevalent due to large vessel stiffness associated with ageing. Calcium channel blocker- or diuretic-based drug treatment is recommended.

In the very elderly, the recommended blood pressure targets may be difficult to achieve due to comorbidity, reduced physiological function and polypharmacy. However, the elderly are most at risk of adverse cardiovascular events and trials have shown that drug therapy is just as effective in advanced age. The HYpertension in the Very Elderly Trial (HYVET) studied patients aged 80 years or more (mean age 83.6 years). It showed a 39% relative reduction in the rate of death from stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes and a 64% reduction in the rate of heart failure for those on active treatment versus placebo. Fewer serious adverse events were reported in the active treatment group so concerns about causing more harm than good are allayed.[11]

Conclusion

Drug therapy is warranted in individuals with a high risk of adverse cardiovascular events. It does not obviate the need for behavioural modification. All classes of antihypertensive drugs have similar efficacy, but specific recommendations are made according to the patient's characteristics. Whichever drug is started, it is important to treat until the target blood pressure is reached. Usually more than one drug is required to reach the target.

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Professor Nelson has participated in trials that have received funding from SmithKline Beecham, AstraZeneca, Bayer, Sanofi-Aventis, Merck Sharpe and Dohme, Pfizer, Servier Laboratories and Bristol-Myers Squibb. He has served on advisory boards for Sanofi-Aventis, Novartis, Schering-Plough and Solvay Pharmaceuticals, prepared educational material for Servier Laboratories, AstraZeneca and Bristol-Myers Squibb and received conference and travel support from Bayer HealthCare AG, Novartis and Sanofi-Aventis.

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Self-test questions

The following statements are either true or false (answers on page 131)

3. Isolated systolic hypertension does not require treatment if the diastolic blood pressure is under 70 mmHg.
4. When there is no response to the initial dose of an antihypertensive drug, it should be titrated to its maximum dose before switching to another drug.

Combination analgesics in adults

***Bridin P Murnion**, Staff Specialist, Drug Health Service, Royal Prince Alfred Hospital, Sydney*

Summary

Many analgesic products contain combinations of different drugs. There are few direct comparisons of these combinations, but several appear to be no more effective than an appropriate dose of one of their individual analgesic components. Many combinations should be avoided because they contain drugs that have significant adverse effects or that do not contribute to the analgesic effect. Some combinations can be obtained without a prescription. Patients may inadvertently overdose themselves if they take several of these products simultaneously.

Key words: aspirin, codeine, dextropropoxyphene, NSAIDs, paracetamol.

(Aust Prescr 2010;33:113–5)

Introduction

There are at least 40 different combination analgesic preparations available in Australia. Most of these are combinations of paracetamol 500 mg with codeine in doses ranging from 8 mg to 30 mg.[1] A number of preparations also contain doxylamine, a sedating antihistamine with anticholinergic effects.[2] There are also other preparations available which contain paracetamol and dextropropoxyphene, aspirin and codeine, aspirin and dihydrocodeine, and ibuprofen and codeine.[1] Internationally, preparations containing paracetamol with other opioids such as oxycodone and tramadol are available.

Regulation

The Australian scheduling of combination analgesics under poisons regulations is determined by the dose of codeine per tablet, the number of tablets in a pack, and the other drugs in the combination (for example doxylamine). All preparations containing 30 mg codeine in combination with paracetamol or aspirin are Schedule 4. They therefore require a prescription. Preparations with doses of codeine 15 mg or less have been available as Schedule 2 (pharmacy medicine) or 3 (pharmacist-only medicine), but from 1 May 2010 they were no longer available in Schedule 2. Combination analgesics containing up to 12 mg codeine are pharmacist-only, and those containing more than 12 mg are prescription-only. The pharmacist-only products are limited to no more than five days of treatment.[3]

Evidence of efficacy

Paracetamol or a non-steroidal anti-inflammatory drug (NSAID) given with a strong opioid such as morphine in a multimodal analgesic regimen for acute pain, reduces the amount of opioid used, improves analgesia and reduces the duration of patient-controlled analgesia.[4] However, data supporting products which combine a weak opioid, such as codeine, with paracetamol or an NSAID, are limited. There is much variability in the dose of weak opioid contained in combination products, and the role of codeine in managing acute pain is unclear. Analgesic guidelines state that 'although codeine is widely used, its place in therapy is uncertain'.[5] The National Prescribing Service (NPS) has stated that 'studies in acute pain suggest only modest additional analgesic efficacy when a weak opioid is added to paracetamol, but a higher rate of adverse effects after repeated doses'.[6] There is consensus that paracetamol is the first-line treatment for many acute pain states.[4–8]

The Oxford Pain group has developed a league table of analgesic efficacy for most common oral analgesics. This uses data from systematic reviews of randomised, double-blind, single-dose studies of patients with moderate to severe pain where the outcome is a reduction of pain by at least 50% in 4–6 hours. Data are expressed as:

- the number of patients who need to be treated (NNT) for one to get 50% relief
- the percentage of patients with at least 50% pain relief (Table 1).

There are limitations to these data. Often the trial sample size is small so there may be wide confidence intervals, they are not head-to-head comparisons, adverse events are not reported and the trials are single-dose studies. The table does not contain information about all the analgesic combinations available in Australia, and includes information about products which are not available here. However, the table provides the best available comparative information.[9]

Paracetamol with codeine

A Cochrane review found that paracetamol with codeine is more effective in acute postoperative pain than paracetamol alone. The NNT to achieve 50% pain relief at 4–6 hours was 2.2 for paracetamol 1 g with codeine 60 mg. Paracetamol 1 g alone has an NNT of 3.8, but paracetamol 600 mg in combination with codeine 60 mg has an NNT of 4.2.[9,10] Although the dose of codeine required to provide any analgesic effect is unclear, it

Table 1

Efficacy of oral analgesics *

Analgesic (mg)	Number of patients in comparison	Percent with at least 50% pain relief	NNT †	Confidence intervals
Paracetamol 1000 + codeine 60	197	57	2.2	1.7–2.9
Paracetamol 600/650 + codeine 60	1123	42	4.2	3.4–5.3
Paracetamol 300 + codeine 30	379	26	5.7	4.0–9.8
Paracetamol 500 + oxycodone IR 10	315	66	2.6	2.0–3.5
Paracetamol 500 + oxycodone IR 5	150	60	2.2	1.7–3.2
Paracetamol 325 + oxycodone IR 5	149	24	5.5	3.4–14.0
Paracetamol 650 + tramadol 75	679	43	2.6	2.3–3.0
Paracetamol 650 + dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate)	963	38	4.4	3.5–5.6
Aspirin 650 + codeine 60	598	25	5.3	4.1–7.4
Aspirin 600/650	5061	38	4.4	4.0–4.9
Codeine 60	1305	15	16.7	11–48
Paracetamol 1000	2759	46	3.8	3.4–4.4
Tramadol 100	882	30	4.8	3.8–6.1
Ibuprofen 200	3248	48	2.7	2.5–2.9

* Modified from the Oxford league table[9]

† Numbers needed to treat (NNT) are calculated for the proportion of patients with at least 50% pain relief over 4–6 hours compared with placebo in randomised, double-blind, single-dose studies in patients with moderate to severe pain

IR Immediate-release formulation

is believed that a minimum dose of 30 mg codeine is required. The majority of combination products available in Australia contain doses of codeine less than this.[5]

In contrast, the National Health and Medical Research Council review of evidence for the management of acute musculoskeletal pain said that there is insufficient evidence to recommend the use of opioids or compound analgesics (paracetamol/codeine combinations) in acute low back pain, acute neck pain, acute shoulder pain or acute knee pain. It reports that, in general, opioids and compound analgesics have a substantially increased risk of adverse effects compared with paracetamol alone.[7]

For dental pain, the most effective approach is to undertake appropriate dental treatment. After dental extraction the efficacy of NSAIDs is superior to that of combinations of paracetamol and codeine.[11,12] The Therapeutic Guidelines: Oral and Dental recommend that if a combination is used, the dose of codeine should be at least 25 mg and suggest that a codeine dose of 60 mg with paracetamol 1 g will be required for severe dental pain.[11]

Dextropropoxyphene

Overdoses of dextropropoxyphene can be fatal. There are concerns about accumulation of a toxic metabolite of dextropropoxyphene in patients with renal impairment.[5] The drug has been withdrawn in the UK and is being withdrawn in New Zealand.

Dextropropoxyphene is a weak opioid, but in combination with paracetamol it provides no increase in analgesia and has more adverse effects than paracetamol alone.[5] The Oxford league table shows that dextropropoxyphene 65 mg in combination with paracetamol 650 mg has an NNT of 4.4.[9]

Doxylamine

There is no evidence that doxylamine has any analgesic efficacy, but this sedating antihistamine may be a component of compound analgesics. Doxylamine may be subject to abuse and combination analgesic preparations containing it cannot be recommended.

Opioids in combination with NSAIDs

While there is a significant body of evidence identifying the efficacy of NSAIDs in acute pain, there are limited data on combining them with opioids. Many NSAIDs, in single-dose studies, show greater efficacy than codeine in combination with paracetamol or codeine in combination with aspirin.[9] Aspirin 650 mg in combination with codeine 60 mg is effective in postoperative pain with an NNT of 5.3 for at least 50% pain relief over 4–6 hours in patients with moderate to severe pain compared with placebo. This appears to be less effective than

a 650 mg dose of aspirin alone (NNT 4.4) but the statistical confidence intervals overlap.[9] Codeine 60 mg may enhance the analgesic effect of ibuprofen 400 mg, however data are lacking to compare the Australian formulation of codeine 12.8 mg with ibuprofen 200 mg to ibuprofen 200 mg alone.[13]

Chronic pain

The evidence for long-term efficacy of opioids in chronic pain is limited. Opioids should only be considered as a component of a multidimensional management plan. In general, opioids other than codeine should be chosen. One exception is osteoarthrosis of the hip, for which there is some evidence for efficacy of codeine.[5]

Opioid analgesics should be avoided in headache because of the risk of dependence and medication overuse headache.[4,8]

Adverse effects and toxicity

Opioids and compound analgesics have a substantially increased risk of adverse effects compared with paracetamol alone.[7] These adverse effects include constipation, nausea, vomiting and drowsiness. The elderly appear to be more susceptible to adverse effects.[5] Abuse of, and dependence on, codeine-containing combination analgesics is a poorly quantified, but likely significant, risk.[14] Codeine is converted to morphine by cytochrome P450 2D6, but 7–10% of the Caucasian population lack this enzyme. These 'poor metabolisers' of codeine will get no analgesic benefit, but may experience adverse effects.[5]

A significant proportion of cases of acute liver failure are from unintentional paracetamol overdose. Many of these patients have taken more than one paracetamol-containing preparation simultaneously.[15]

Conclusion

In summary, for acute postoperative pain there is evidence of efficacy for paracetamol 1 g with codeine 60 mg, and some evidence for paracetamol combined with codeine in hip osteoarthroses. Current guidelines do not support the use of paracetamol and codeine combination products in other acute or chronic pain states. There are limited data for doses of codeine less than 60 mg in combination with paracetamol, and current data suggest that paracetamol alone has greater efficacy than paracetamol combined with codeine at doses under 60 mg. Current evidence shows improved analgesia with codeine 60 mg and ibuprofen 400 mg compared to ibuprofen alone, but there are minimal data for lower doses. Indirect comparisons show that the combination of aspirin and codeine may be less efficacious than aspirin alone and therefore the combination cannot be recommended. Given the lack of documented analgesic efficacy of low-dose codeine preparations, rescheduling of codeine in Australia is unlikely to impact significantly on analgesic options, but may reduce the harms from overuse.

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See **Dental note** p.107, and information for consumers on this article at www.australianprescriber.com

Conflict of interest: none declared

Managing constipation in adults

***Warwick Selby**, Clinical Associate Professor, Department of Medicine, University of Sydney, and Director of Endoscopic Services, Royal Prince Alfred Hospital; and **Crispin Corte**, Senior Gastroenterology Registrar, Royal Prince Alfred Hospital, Sydney*

Summary

Patients complaining of constipation require a history and examination and possibly simple investigations to find out if their problem is secondary to other conditions or drugs. If there is no underlying cause, non-drug treatments such as increasing dietary fibre should be recommended. Drug treatment can be considered if the constipation persists. Bulking agents can be tried and then osmotic laxatives. Stimulant laxatives are available, but their long-term use is not recommended. Specialist assessment should be considered if the constipation remains refractory to treatment.

Key words: colon, laxatives.

(Aust Prescr 2010;33:116–9)

Introduction

Chronic constipation leads to a considerable loss of quality of life and increases healthcare costs. It is also a common reason for primary care visits and referrals to gastroenterologists.

The prevalence of constipation varies with the definition used. The Rome III criteria (see Box 1) are a useful definition for chronic functional constipation.[1] Many people who complain of constipation do not meet these criteria. Simpler definitions include patients with fewer than three bowel movements per week, or those who report a consistent difficulty with defecation such as hard or infrequent stools, prolonged time spent on the toilet or a sense of incomplete emptying.

Recent Australasian epidemiological studies of constipation report prevalences of 6–30%.[2] Predisposing factors include female sex, increasing age, low socioeconomic status, depression and a history of sexual abuse.

Assessment

Being alert to alarm symptoms (see Box 2) is important as they may point towards an underlying organic cause such as colorectal neoplasia, intestinal obstruction or inflammatory bowel disease. Chronic constipation in the absence of these alarm symptoms can still be due to other secondary causes. These include endocrine diseases such as diabetes mellitus and hypothyroidism, and neurological injuries and diseases such as multiple sclerosis and Parkinson's disease. In addition, perineal problems such as fissures and haemorrhoids may lead to constipation. A variety of drugs can also cause or aggravate constipation (see Box 3).

Underlying causes may be identified by a thorough history and clinical examination (including rectal examination). There is no

Box 1

Rome III criteria for chronic constipation[1]

Presence of two or more of the following:

- straining during at least 25% of bowel movements
- lumpy or hard stools in at least 25% of bowel movements
- sensation of incomplete evacuations for at least 25% of bowel movements
- sensation of anorectal blockage for at least 25% of bowel movements
- manual manoeuvres to facilitate at least 25% of bowel movements
- fewer than three bowel movements each week.

Loose stools are rarely present without laxatives.

These criteria must have been present for the last three months, with symptom onset at least six months before diagnosis.

Box 2

Constipation – alarm symptoms for more serious conditions

Acute or recent constipation

Obstipation

Rectal loss of blood, melaena or mucus

Weight loss

Fever

Rectal pain

Change in stool calibre

Anorexia, nausea, vomiting

Family history of inflammatory bowel disease or colorectal cancer

Aged over 50 years

Box 3

Constipating drugs

Analgesics
Opioids
Non-steroidal anti-inflammatory drugs

Anticholinergics
Antihistamines
Antispasmodics
Antidepressants
Antipsychotics

Neurally active drugs
Antihypertensives
Ganglion blockers
Vinca alkaloids
Thalidomide
Calcium channel blockers
$5HT_3$ antagonists

Iron supplements

Antacids containing aluminium

evidence available to support the routine use of investigations, if there are no alarm symptoms.[3] If further investigation is needed, begin with simple tests such as complete blood count, thyroid function, calcium, electrolytes, glucose and urinalysis.

Physiological testing is required only infrequently, in those with symptoms not responding to treatment and who do not have a secondary cause for their constipation. Colonic transit testing is performed by either monitoring the progress of ingested radio-opaque markers on plain abdominal radiographs, or (less commonly) using scintigraphy. These tests may identify slow transit if present, but do not specifically alter management. Patients with predominantly anorectal symptoms may benefit from studies such as balloon expulsion testing to confirm a defecatory defect. Defecography is rarely needed and only if there is suspicion of a structural abnormality affecting defecation.

Management

Secondary causes of constipation should be treated. If possible, the concurrent use of constipating drugs should be avoided. Most patients will have idiopathic constipation, or constipation-predominant irritable bowel syndrome. The initial approach in this condition should be diet and non-drug treatment. If this fails, drugs can be used.

Non-drug treatment

Reassurance can be offered if there are no alarm symptoms. Simple education about a normal stool habit may help. The timing of bowel motions should be as regular as possible. Defecation should not be postponed unnecessarily when the urge arises. Patients can be reminded that colonic motility is maximal after meals and that this is a good time to try to plan regular defecation. If the disorder is defecatory, then biofeedback is effective in up to 75% of cases.

There is a reliable dose-response between fibre and water intake and stool bulk and frequency. A dietary history will determine whether there is sufficient fibre in the diet in the form of cereals, grains, and fruit and vegetables. Increasing dietary fibre to the recommended daily intake of approximately 30 g or the use of fibre supplements such as psyllium should help in those patients with fibre deficiency. Adequate daily fluid intake is also important to maximise the benefit of fibre. However, increasing fibre intake beyond the required amount results in bloating or flatulence in many patients without relieving constipation, and may even aggravate it. Similarly, merely increasing the daily fluid intake in the absence of adequate fibre will not improve constipation.

Increasing physical activity can promote colonic motility, so an active lifestyle can be encouraged. As constipation may be exacerbated by stress and depression, these factors should be addressed if they are present.

Pharmacological measures

Many patients who present with constipation will have already tried a variety of non-prescription remedies. Enquire about the use of these remedies before deciding the best approach to treatment.

The numerous agents commonly used to treat constipation can be classified according to their mechanism of action (Table 1). Their relative efficacy and tolerability has generally not been well studied. The choice of treatment is therefore based on the mechanism of action, required onset, duration of action and patient preference. Trial and error is often required to determine the optimal management plan.

Bulking agents

Hydrophillic organic polymers (including psyllium and bran) function by sequestering extra water in the stools. The resulting increase in the volume of luminal contents is thought to stimulate intestinal activity and thereby enhance the speed of transit. A change in stool consistency associated with the increased water content may also ease defecation. The bulking agents are often the first line of treatment. However, fermentation of fibre in the colon can result in bloating and flatulence, particularly if the patient's diet already has sufficient fibre.

Osmotic laxatives

The capacity of the intestine to absorb some molecules and ions, such as magnesium salts, is limited. Other molecules, such as lactulose and sorbitol, are completely unabsorbed. To maintain an iso-osmolar state, these substances draw water

Table 1

Treatments for constipation in adults

Constituent	Dose	Time to onset
Bulking agents		
Ispaghula	1 sachet or teaspoon in water	24 hours, maximum effect at 2–3 days
Psyllium (multiple formulations and additives)	Per packet* – two teaspoons 1–3/day	24 hours, maximum effect at 2–3 days
Sterculia	1–2 teaspoons 1–2/day	24 hours, maximum effect at 2–3 days
Osmotic agents		
Oral		
Lactulose	15–30 mL 1–2/day	1–2 days
Macrogol (PEG 3350) with electrolytes	1–2 sachets each in 125 mL water, can give up to 8 for faecal impaction	Variable
Magnesium sulfate	15 g in 250 mL water daily	1 hour
Sorbitol liquid	20 mL 1–3/day	2–3 days
Sodium phosphate	Per packet*	½–6 hours
Sodium picosulfate (multiple formulations and additives)	Per packet*	Variable
Rectal		
Sodium phosphate	133 mL single dose	2–5 minutes
Sodium citrate/sorbitol/sodium lauryl sulfoacetate	5 mL	30 minutes
Stool softeners		
Docusate	2 x 120 mg tablets daily	1–3 days
Stimulant laxatives		
Oral		
Bisacodyl	1–2 x 5 mg tablets daily	6–12 hours
Senna/sennosides (multiple formulations and additives)	Per packet*	6–12 hours
Rectal		
Bisacodyl (multiple formulations)	Per packet*	15–60 minutes
Lubricants		
Oral		
Paraffin emulsion	15–30 mL two hours before lying down	2–3 days
Rectal		
Glycerol suppository	1 daily	5–30 minutes

* doses as recommended on packaging

into the intestinal lumen resulting in a laxative effect. Osmotic laxatives can be tried if the bulking agents are not appropriate or are ineffective.

The non-absorbable sugars are fermented in the colon so they can cause bloating, distension and flatulence which may limit their use. They should not be used by people with diabetes. Long-term use of magnesium salts is not recommended, particularly in patients with renal impairment.

Another approach is the use of large osmotically active polymers such as polyethylene glycol (PEG or macrogol). They are made iso-osmolar with intestinal contents so the water ingested with them is retained in the gut. The polymers are not absorbed, making them more suitable for long-term use in low volume. They can be used if simpler measures are ineffective, and are also used to prepare patients for colonoscopy.

Stimulant laxatives

Stimulant laxatives are often combined with stool softeners and may be useful in patients with poor colonic motility.

Diphenylmethane derivatives inhibit water absorption after activation, by endogenous esterases in the case of bisacodyl, or by colonic flora in the case of sodium picosulfate. These laxatives can precipitate cramping and electrolyte wasting.

Anthraquinones are available as mixtures of compounds (such as senna) and lead to water secretion following mucosal contact as well as direct stimulation of enteric nerve endings. There is

a suggestion of a damaging effect on the colonic mucosa and increasing doses are often needed over time. The chronic use of stimulant laxatives should be avoided.

Stool softeners and lubricants

Stool softeners such as docusate are detergents that facilitate the interaction between colonic water and stool. Lubricants, such as paraffin, have no pharmacological interaction with colonic mucosa, but alter stool composition in addition to their lubricating effect. Prolonged use of paraffin may cause malabsorption of fat soluble vitamins and should be used only in special circumstances, for example in some patients with cystic fibrosis. Liquid paraffin should not be used by patients at risk of aspiration.

Neuromuscular drugs

The benefit of these drugs is in their known adverse effect of diarrhoea, but they are not available primarily for this purpose and there are no clinical trials supporting their use. Local chloride channel activators (lubiprostone) and $5HT_4$ receptor modulators like cisapride, prucalopride and tegasarod, are not available in Australia.

Methylnaltrexone

Methylnaltrexone is a peripherally acting mu opioid receptor antagonist. It is administered subcutaneously, and is used in patients with opioid-induced constipation. It is only approved for use in the setting of palliation, and is contraindicated in malignant bowel obstruction.

Pregnancy

Constipation is a common problem in pregnancy and iron supplements may also contribute to this. Fibre supplements, bisacodyl, lactulose and docusate all have reliable safety and efficacy in pregnancy. Although stimulant laxatives have been shown to be more effective, there is less certainty about their safety.

Conclusion

When non-pharmacological measures fail, consider prescribing a bulking agent. If this does not help then one of the osmotic laxatives can be tried, although there is little evidence to guide therapy, and there are failures with all approaches. The dose of laxative may need to be titrated to balance the benefit with any adverse effects. Long-term therapy with bulking agents, polyethylene glycol or lactulose is considered to be safe.

Stimulant laxatives can be used either alone or in combination with osmotic laxatives in patients with resistant chronic constipation. Long-term stimulant laxatives are avoided as they may induce melanosis coli, tolerance or cathartic colon and there is little evidence for their efficacy.

Treatment refractory constipation should prompt reconsideration of secondary causes. Referral to specialist services and physiological testing may be needed.

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Conflict of interest: none declared

There is information for consumers on this article at www.australianprescriber.com

Self-test questions

The following statements are either true or false (answers on page 131)

5. Long-term use of laxatives containing magnesium should be avoided in patients with renal disease.
6. Liquid paraffin should be avoided in patients with risk of aspiration.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Medicines Safety Update No. 4; 2010

Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it and sign up for free Medicines Safety Update email alerts on the TGA website at www.tga.gov.au/adr/msu.htm

In this issue:

Varenicline (Champix): an update

Dr Jennifer Elijah, Evaluator, Office of Product Review

Summary

Psychiatric symptoms, including suicidal behaviour, continue to be reported with varenicline. We ask health professionals to include relevant information from the patient's history in adverse reaction reports to help in our assessment of cases, and remind them to discuss the possibility of these events with patients and their families.

The TGA has previously reported Australian experience with varenicline (Champix) up to October 2008.[1] In this update, we describe experience with varenicline to May 2010 – in particular, adverse reaction reports of psychiatric symptoms.

Varenicline is available on the Pharmaceutical Benefits Scheme (PBS) as an authority item for people in a comprehensive support and counselling program for smoking cessation. More than 900 000 PBS prescriptions for varenicline have been dispensed since January 2008.

Psychiatric symptoms reported with varenicline

To May 2010 the TGA had received 1025 reports of suspected adverse reactions to varenicline, 691 (67%) of which describe psychiatric symptoms such as depression, agitation, anxiety, altered mood and aggression. There were reports of 206 suicide-related events in people taking varenicline, including 15 completed suicides.

We remind health professionals to discuss these possible adverse effects with patients taking or considering varenicline and their families, and to provide patients with the Consumer Medicines Information leaflet. Health professionals should provide advice to patients and their families about how to recognise and respond to these possible adverse effects.

What to include in adverse reaction reports

We ask health professionals to continue to report suspected adverse reactions to varenicline to the TGA. Please include in reports relevant information such as the patient's history of mental illness, concomitant psychotropic medicines and any reactions to previous quit attempts (See box). This information helps us to review cases and make a reasonable assessment of causality – particularly because the association of varenicline and neuropsychiatric symptoms may be confounded by factors such as the effects of nicotine withdrawal, the association of smoking and psychiatric conditions, and the effects of changes in smoking status on blood levels of some antipsychotics.

Reference

1. Varenicline: the Australian experience so far. Aust Adv Drug React Bull 2008;27:22.

Box

Patient information to include in reports of possible adverse reactions to varenicline

- smoking, alcohol and substance use status
- any previous reactions to smoking cessation
- history of pre-existing psychiatric/mental illness
- past history of suicidal ideation/suicide attempt
- history of any recent psychosocial stresses
- history of concomitant medication especially psychotropic medications

Australian experience with non-adjuvant H1N1 vaccine (Panvax and Panvax Junior)

Dr Jane Cook, Senior Medical Officer, Office of Product Review

Summary

The H1N1 influenza vaccination program used strategies to encourage consumers and health professionals to report adverse events to allow the TGA to closely monitor safety of the vaccine. Information is now available about the number and types of adverse reactions reported during the first six months of the program.

The Australian national immunisation program with the non-adjuvant H1N1 vaccine (Panvax and Panvax Junior) began on 30 September 2009. The program was different from other national vaccination programs in several ways, including that it used strategies to stimulate adverse event reporting so that the TGA could closely monitor vaccine safety.

The program was aimed at certain groups at higher risk of exposure to H1N1 (such as healthcare workers) and those vulnerable to more severe outcomes (pregnant women, indigenous people and people with underlying chronic medical conditions) but was promoted and available to all Australians. Immunisation was provided via state and territory immunisation clinics and general practices.

Information provided about vaccine safety and reporting mechanisms

The TGA worked closely with expert committees such as the Australian Technical Advisory Group on Immunisation (ATAGI) and the National Immunisation Committee (a subgroup of the Australian Health Protection Principal Committee) to provide information to health practitioners and consumers on how to report adverse events. The TGA set up a telephone service to take adverse event reports and provided a web reporting tool on its website. Details of both ways to report adverse events and information about managing common, expected adverse effects of vaccination were included in fact sheets and consent forms provided to consumers (Fig. 1).

As the aim of a pandemic program is to immunise a large number of people as efficiently as possible, multidose vials were used. Multidose vials are not routinely used in Australia, although they are used in the United States to administer seasonal trivalent influenza vaccine. Information was developed to reassure consumers of the safety of thiomersal, the preservative in the vials, for pregnant women and children. Fact sheets were developed by ATAGI and distributed via the Department of Health and Ageing's Health Emergency website (www.healthemergency.gov.au) and healthcare provider networks.

Patterns of reporting

In the first six months of the program, from 30 September 2009 to 31 March 2010, approximately eight million doses of Panvax and 330 000 doses of Panvax Junior were distributed in Australia. During this period, the TGA received 1614 reports of adverse events associated with H1N1 vaccination.

The highest number of reports was received in October 2009, when there were 696 adverse event reports. By January 2010 numbers had fallen to around 80 reports per month. A second, smaller peak in reporting occurred in March, with 145 reports (Fig. 2). The TGA suspects the second peak was caused by a

Fig. 1

Information about adverse events included in the vaccination consent form and fact sheet

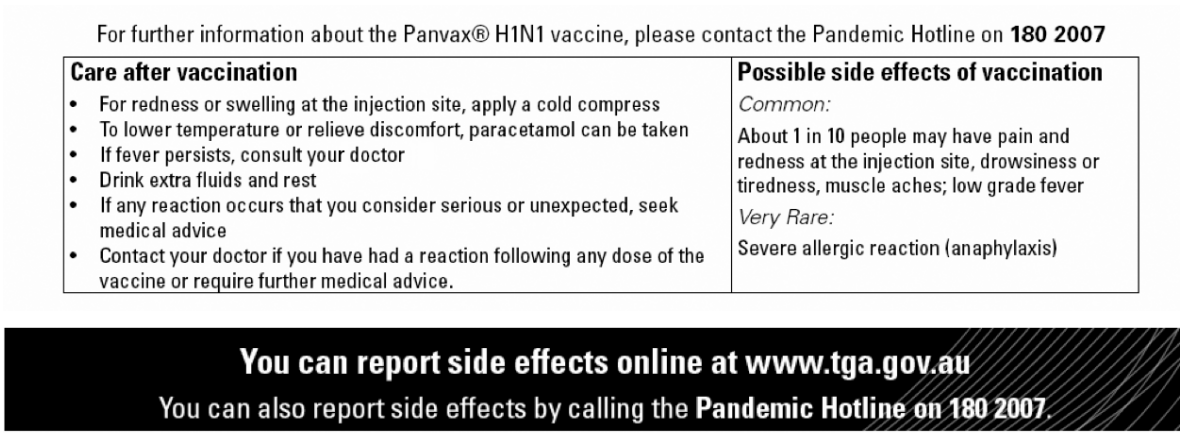
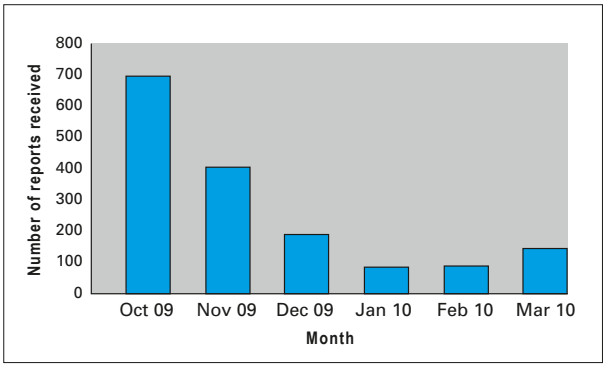


Fig. 2

Adverse event reports associated with H1N1 vaccination during the first six months of the Australian vaccination program



second wave of promotion of the program by the Department of Health and Ageing, the start of school-based programs in some states and territories, and catch-up reporting following the vacation period.

Types of reactions reported

Most of the 1614 reports received were mild and common problems such as headache, gastrointestinal upset, and injection-site soreness, swelling or redness (Table 1). Most of the adverse effects reported were well recognised and listed in the Product Information for Panvax and Panvax Junior.

Neurological events

Several neurological adverse events of special interest were closely monitored. One of the concerns raised was a possible association between Guillain-Barré syndrome and vaccination. This concern arose from the observation that in the United States the 1976 influenza vaccine was associated with an excess risk of Guillain-Barré syndrome of nine in every one million vaccinees in the six weeks following vaccination.[1] This association has not been seen since. The TGA convened an expert panel to assist in developing case definitions and clinical follow-up templates and to review cases. In total, 10 reports of Guillain-Barré syndrome were received by the TGA in the first six months of the program. This is within the background rate that would be expected for an unvaccinated population.

Allergy and anaphylaxis

The occurrence of allergy and anaphylaxis was also closely monitored by the TGA. Anaphylaxis and allergic reactions are not predictable and can occur in anyone regardless of whether they have a history of allergy or not. There were nine cases of anaphylaxis reported and all recovered without sequelae.

There was one case of anaphylaxis reported in a person with a latex allergy who had previously received seasonal trivalent vaccines without any allergic response. The TGA investigated whether latex may have been coming into contact with the vaccine, including commissioning studies in Europe. Investigations showed that latex was not detectable in the vaccine, even when the syringe was damaged or abnormal or the rubber bung of the syringe was crushed.

Convulsions

The number of reports of convulsion associated with H1N1 vaccination is of particular interest. The 2010 seasonal trivalent influenza vaccination program was suspended for children five years and under, following a higher than usual number of reports of febrile convulsion associated with vaccination. In the first six months of the H1N1 vaccination program there were seven reports of febrile convulsion, all of which were in children under five years. Two of these

Table 1

Commonly reported reactions to H1N1 vaccination during the first six months of the Australian vaccination program

Reaction	Number of cases	% reports containing one or more of these terms
Pain (excluding injection-site pain)	388	24%
Malaise, lethargy, fatigue, asthenia	360	22%
Influenza-like illness, cough, rhinorrhoea, oropharyngeal pain	346	21%
Vomiting, diarrhoea	317	20%
Headache	303	19%
Pyrexia	280	17%
Rash (any type), pruritus, urticaria	269	17%
Injection-site reaction or injection-site pain	240	15%
Nausea	203	12.5%

cases occurred in association with varicella vaccine. The Product Information documents for Panvax and Panvax Junior include the occurrence of convulsions as an uncommon event, occurring in 1 in 1000 to 1 in 10 000 cases. More than 300 000 doses of Panvax Junior have been distributed, and so these figures provide reassurance that the non-adjuvant H1N1 vaccine does not produce an excess risk of convulsions in children.

Reference

1. Australian Technical Advisory Group on Immunisation (ATAGI) advice regarding influenza, influenza vaccines and Guillain-Barré Syndrome. Canberra: Australian Government Department of Health and Ageing; 2009. www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/2723D54E78BF5739CA2576400027E1E9/$File/ATAGI-Infl_FluVac_GBS-Advice_091009.pdf [cited 2010 Jul 7]

New structural arrangements

The TGA officially launched a new organisational structure on 1 July 2010. This new structure will support the TGA's delivery of appropriate, consistent, effective and efficient regulation into the future.

Postmarketing safety functions for all types of therapeutic products are managed by the Office of Product Review, which is part of the Monitoring and Compliance Group.

The implementation of the new structure is being carefully managed to ensure that current regulatory activities are maintained. The main contact points for reporting suspected reactions to medicines are unchanged, and information for health professionals and consumers – such as alerts, advisories and *Medicines Safety Update* – will continue to be published as usual.

Detailed information on the new structural arrangements is available at www.tga.gov.au/about/structure-new.htm

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 Product Review, phone 1800 044 114.

Reports can also be submitted:

online www.tga.gov.au and click on 'Report a problem' on the left
by fax 02 6232 8392
by email ADR.Reports@tga.gov.au

For further information from the Office of Product Review:
Phone 1800 044 114 Fax 02 6232 8392 Email ADR.Reports@tga.gov.au

The interpretation of arterial blood gases

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Summary

Arterial blood gas analysis is used to measure the pH and the partial pressures of oxygen and carbon dioxide in arterial blood. The investigation is relatively easy to perform and yields information that can guide the management of acute and chronic illnesses. This information indicates a patient's acid–base balance, the effectiveness of their gas exchange and the state of their ventilatory control. Interpretation of an arterial blood gas result should not be done without considering the clinical findings. The results change as the body compensates for the underlying problem. Factors relating to sampling technique, specimen processing and environment may also influence the results.

Key words: acid–base disorders, pulmonary function tests.

(Aust Prescr 2010;33:124–9)

Introduction

Arterial blood gas analysis is a common investigation in emergency departments and intensive care units for monitoring patients with acute respiratory failure. It also has some application in general practice, such as assessing the need for domiciliary oxygen therapy in patients with chronic obstructive pulmonary disease. An arterial blood gas result can help in the assessment of a patient's gas exchange, ventilatory control and acid–base balance. However, the investigation does not give a diagnosis and should not be used as a screening test. It is imperative that the results are considered in the context of the patient's symptoms.

While non-invasive monitoring of pulmonary function, such as pulse oximetry, is simple, effective and increasingly widely used, pulse oximetry is no substitute for arterial blood gas analysis. Pulse oximetry is solely a measure of oxygen saturation and gives no indication about blood pH, carbon dioxide or bicarbonate concentrations.

Arterial puncture

Blood is usually withdrawn from the radial artery as it is easy to palpate and has a good collateral supply. The patient's arm is placed palm-up on a flat surface, with the wrist dorsiflexed at 45°. A towel may be placed under the wrist for support. The puncture site should be cleaned with alcohol or iodine, and a local anaesthetic (such as 2% lignocaine) should be infiltrated. Local anaesthetic makes arterial puncture less painful for the patient and does not increase the difficulty of the procedure.[1] The radial artery should be palpated for a pulse, and a pre-heparinised syringe with a 23 or 25 gauge needle should be inserted at an angle just distal to the palpated pulse (Fig. 1). A small quantity of blood is sufficient. After the puncture, sterile gauze should be placed firmly over the site and direct pressure applied for several minutes to obtain haemostasis. If repeated arterial blood gas analysis is required, it is advisable to use a different site (such as the other radial artery) or insert an arterial line.

To ensure accuracy, it is important to deliver the sample for analysis promptly. If there is any delay in processing the sample, the blood can be stored on ice for approximately 30 minutes with little effect on the accuracy of the results.

Complications of arterial puncture are infrequent. They include prolonged bleeding, infection, thrombosis or arteriospasm.

Fig. 1

Performing an arterial puncture

Interpreting a blood gas result

The automated analysers measure the pH and the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in arterial blood. Bicarbonate (HCO_3^-) is also calculated (Box 1). These measurements should be considered with the patient's clinical features (Table 1).

pH

The pH determines the presence of acidaemia or alkalaemia. If the body has compensated for the disorder, the pH may be in the normal range.

$PaCO_2$

The $PaCO_2$ reflects the state of alveolar ventilation. An elevated $PaCO_2$ reflects alveolar hypoventilation, whereas a decreased $PaCO_2$ reflects alveolar hyperventilation. Acute changes in $PaCO_2$ will alter the pH. As a general rule, a low pH with a high $PaCO_2$ suggests a respiratory acidosis, while a low pH with a low $PaCO_2$ suggests a metabolic acidosis.

Box 1

Reference ranges for arterial blood gases

pH	7.35 – 7.45	
PaO_2	80 – 100* mmHg	10.6 – 13.3 kPa
$PaCO_2$	35 – 45 mmHg	4.7 – 6.0 kPa
HCO_3^-	22 – 26 mmol/L	
Base excess	–2 – +2 mmol/L	

Reference ranges for venous blood gases

pH	7.32 – 7.43
PvO_2	25 – 40 mmHg
$PvCO_2$	41 – 50 mmHg
HCO_3^-	23 – 27 mmol/L

* age and altitude dependent (see text)

Kilopascals: to convert pressures to kPa, divide mmHg by 7.5

Table 1

Correlating arterial blood gas results with clinical features

	Metabolic imbalances		Respiratory imbalances	
	Metabolic acidosis	**Metabolic alkalosis**	**Respiratory acidosis**	**Respiratory alkalosis**
pH	↓	↑	↓	↑
$PaCO_2$	N (uncompensated) ↓ (compensated)	N (uncompensated) ↑ (compensated)	↑	↓
HCO_3^-	↓	↑	N (uncompensated) ↑ (compensated)	N (uncompensated) ↓ (compensated)
Base excess	↓	↑	N / ↑	N / ↓
Clinical features	Kussmaul-type breathing (deeper, faster respiration), shock, coma	Paraesthesia, tetany, weakness	Acute: air hunger, disorientation Chronic: hypoventilation, hypoxia, cyanosis	Acute: hyperventilation, paraesthesia, light-headedness Chronic: hyperventilation, latent tetany
Common causes	With raised anion gap: diabetic ketoacidosis, lactic acidosis, poisons (e.g. ethylene glycol), drug overdoses (paracetamol, aspirin, isoniazid, alcohol) With normal anion gap: diarrhoea, secretory adenomas, ammonium chloride poisoning, interstitial nephritis, renal tubular acidosis, acetazolamide administration	Vomiting, prolonged therapy with potassium-wasting diuretics or steroids, Cushing's disease, ingestion/ overdose of sodium bicarbonate (e.g. antacids)	Hypoventilation – chronic lung disease with CO_2 retention, e.g. chronic obstructive pulmonary disease, respiratory depression from drugs (e.g. opioids, sedatives), severe asthma, pulmonary oedema	Hyperventilation – anxiety, pain, febrile illness, hypoxia, pulmonary embolism, pregnancy, sepsis

N = within normal range ↑ = increased ↓ = decreased

There is a delayed response of $PaCO_2$ to an acute change. Increases in $PaCO_2$ occur relatively slowly, as the body's overall CO_2 stores are very large (approximately 20 L) and the volume of CO_2 generated by metabolism (200 mL/min) makes little overall difference. For instance, during a breath-hold, the $PaCO_2$ rises at a rate of only 2–3 mmHg per minute, hence patients with a very high $PaCO_2$ usually have a long-standing disorder. Accordingly, even when treated the $PaCO_2$ may take a long time to return to normal.

PaO_2

The state of arterial blood oxygenation is determined by the PaO_2. This reflects gas exchange in the lungs and normally the PaO_2 decreases with age. This is due to decreased elastic recoil in the lungs in the elderly, thereby yielding a greater ventilation-perfusion mismatch. The expected PaO_2 when breathing air at sea level can be calculated with the equation $PaO_2 = 100 – (age \times 0.25)$. Consequently, a PaO_2 of 75 mmHg, which may be of concern in a young person, is usually unremarkable in an 85-year-old.

A PaO_2 that is less than expected indicates hypoxaemia. This can result from hypoventilation or a mismatch of ventilation and perfusion. If alveolar ventilation is adequate (that is, $PaCO_2$ is normal), then the hypoxaemia is almost certainly caused by a ventilation-perfusion disturbance. The nature of the hypoxaemia can be further assessed by the difference between the alveolar and arterial oxygen tensions.

The alveolar–arterial oxygen tension difference

If an arterial blood gas result shows hypoxaemia (low PaO_2) and inadequate alveolar ventilation (high $PaCO_2$), it must be determined whether the hypoxaemia is related to hypoventilation, or is secondary to a disturbance in ventilation-perfusion, or both. This is assessed by calculating the difference between the alveolar (PAO_2) and arterial (PaO_2) oxygen tensions (see Box 2).

The alveolar–arterial difference, or gradient, can be estimated only if the oxygen fraction of inspired air (FiO_2, usually 0.21 on room air), barometric pressure and water vapour pressure are known. A normal reference range is 5–15 mmHg. The difference, expressed as $P(A–a)O_2$, increases with age, cigarette smoking and increasing FiO_2. An expected $P(A–a)O_2$ can be calculated using the formula $P(A–a)O_2 = 3 + (0.21 \times \text{patient's age})$.

All causes of hypoxaemia, apart from hypoventilation, increase the alveolar-arterial difference. In a patient breathing room air, a $P(A–a)O_2$ greater than 15 mmHg suggests a ventilation-perfusion mismatch related to disease of the airways, lung parenchyma or pulmonary vasculature. However, the result is non-specific in defining the actual pathology and again the patient's clinical features are essential for diagnosis.

Box 2

The alveolar–arterial oxygen gradient

$P(A–a)O_2 = PAO_2 – PaO_2$

PaO_2 = arterial oxygen tension

PAO_2 = alveolar oxygen tension

$PAO_2 = FiO_2(P_B – P_{H2O}) – 1.2(PaCO_2)$

FiO_2 = oxygen fraction in inspired air

P_B = barometric pressure (760 mmHg at sea level)

P_{H2O} = water vapour tension (47 mmHg at 37° C)

Normal value <15 mmHg

Bicarbonate

Bicarbonate is a weak base that is regulated by the kidneys as part of acid–base homeostasis. The HCO_3^- measured in arterial blood reflects the metabolic component of arterial blood. Together, CO_2 and HCO_3^- act as metabolic and respiratory buffers respectively. They are related via the equation:

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

Compensatory changes

For any disturbance of gas tensions in arterial blood, a compensatory system exists to maintain homeostasis. In a metabolic disorder, where HCO_3^- may be retained or excreted by the kidneys, respiratory compensation can occur almost immediately to alter the rate and depth of ventilation to retain or remove CO_2. This occurs due to the exquisite sensitivity of chemoreceptors in the medulla to carbonic acid (H_2CO_3) or H^+. Renal compensation in response to a respiratory disorder takes much longer, sometimes between three and five days, to retain or remove HCO_3^- as required.

As a general rule, when compensation is present the arterial blood gas result shows two imbalances – derangement of both HCO_3^- and $PaCO_2$. A clue to which imbalance is the primary disturbance is obtained from the pH. If pH is leaning toward acidosis or alkalosis, then the parameter that matches the pH trend (that is, is increased or decreased corresponding to pH) is the primary problem and the other is due to compensation.

The base excess

The metabolic component of the acid–base balance is reflected in the base excess. This is a calculated value derived from blood pH and $PaCO_2$. It is defined as the amount of acid required to restore a litre of blood to its normal pH at a $PaCO_2$ of 40 mmHg. The base excess increases in metabolic alkalosis and decreases (or becomes more negative) in metabolic acidosis, but its utility in interpreting blood gas results is controversial.

While the base excess may give some idea of the metabolic nature of a disorder, it may also confuse the interpretation. The alkalaemia or acidaemia may be primary or secondary to respiratory acidosis or alkalosis. The base excess does not take

into account the appropriateness of the metabolic response for any given disorder, thus limiting its utility when interpreting results.

Anion gap

The anion gap assists with the diagnosis of metabolic acidosis (Box 3). This difference between the concentrations of measured anions and cations increases with dehydration and decreases with hypoalbuminaemia. The gap also widens if there is an increase in the concentration of unmeasured anions such as ketones and lactate.

Factors influencing blood gas results

A number of sampling and environmental factors may affect the result of the analysis. Delayed processing of the sample may yield a falsely low PaO_2, as the delay allows leucocytes to consume oxygen. This can be avoided by prompt transport of the sample on ice.

Air bubbles introduced when performing the arterial puncture can also cause a falsely high PaO_2 and a falsely low $PaCO_2$.[2] This can be avoided by gently removing air bubbles within the specimen immediately after collection without agitating the sample.

Body temperature can also affect arterial blood gas tensions. This is relevant in febrile or hypothermic patients, so body temperature should be recorded at the time of collection.[3]

Box 3

The anion gap concept

- the anion gap is an artificial concept that may indicate the cause of a metabolic acidosis
- it represents the disparity between the major measured plasma cations (sodium and potassium) and the anions (chloride and bicarbonate)
- when calculating the anion gap, potassium is usually omitted from the calculation thus:
  $Gap = Na^+ – (Cl^- + HCO_3^-)$
- the anion gap is normally between 8 and 16 mmol/L
- a raised anion gap indicates an increased concentration of lactate, ketones or renal acids and is seen in starvation and uraemia
- a raised anion gap is seen in overdoses of paracetamol, salicylates, methanol or ethylene glycol
- a normal anion gap is seen if a metabolic acidosis is due to diarrhoea or urinary loss of bicarbonate

Mixed acid–base disorders

It is possible to have a mixed respiratory and metabolic disorder that makes interpretation of an arterial blood gas result difficult. As a general rule, when a normal pH is accompanied by an abnormal $PaCO_2$ or HCO_3^- then a mixed metabolic-respiratory disorder exists. Table 2 provides some common clinical examples of mixed respiratory and metabolic disturbances, and

Table 2

Examples of mixed acid–base disorders

Mixed metabolic/ respiratory disturbance	Example
Respiratory acidosis and metabolic acidosis	A patient with acute pulmonary oedema after an acute myocardial infarct Mechanism: poor cardiac circulation (causing a lactic acidosis – metabolic acidosis) with concurrent poor alveolar ventilation (due to pulmonary oedema) – causing CO_2 retention and a concomitant respiratory acidosis
Respiratory alkalosis and metabolic alkalosis	A patient with hepatic cirrhosis who is given diuretics Mechanism: patients with hepatic cirrhosis can experience the phenomenon of the hepatopulmonary syndrome where the major symptom is dyspnoea (causing a respiratory alkalosis), while diuretics can cause a decrease in blood volume, which stimulates the renin-angiotensin-aldosterone system, increasing the exchange between Na^+ and K^+ or H^+ at the distal tubule, resulting in an increase in bicarbonate concentration and a metabolic alkalosis
Respiratory acidosis and metabolic alkalosis	A patient with long-standing chronic obstructive pulmonary disease who is given diuretics for concomitant heart failure Mechanism: long-standing air flow limitation may cause chronic hypercapnia and respiratory acidosis via impaired CO_2 excretion, while diuretics can cause a decrease in blood volume, which stimulates the renin-angiotensin-aldosterone system, increasing the exchange between Na^+ and K^+ or H^+ at the distal tubule, resulting in an increase in bicarbonate concentration and a metabolic alkalosis
Respiratory alkalosis and metabolic acidosis	A patient with chronic renal failure who begins to hyperventilate secondary to anxiety Mechanism: chronic renal failure causes a metabolic acidosis by uraemia and failure to excrete acids while the respiratory alkalosis results from blowing off excess CO_2 due to alveolar hyperventilation
Metabolic acidosis and metabolic alkalosis	A patient with chronic renal failure who suffers from severe intractable vomiting Mechanism: chronic renal failure causes a metabolic acidosis by uraemia and failure to excrete acids while a concurrent metabolic alkalosis results from the depletion in the body stores of H^+ and Cl^- through vomiting

Fig. 2

Interpreting acidaemia on an arterial blood gas result

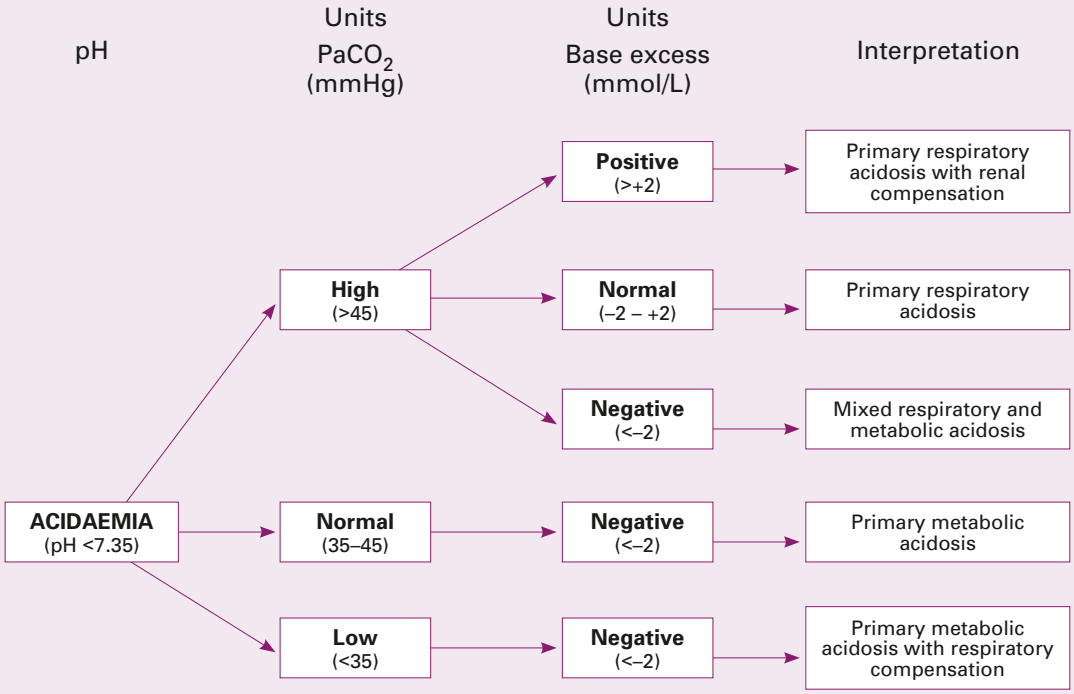

Image adapted from reference 4 with permission

Fig. 3

Interpreting alkalaemia on an arterial blood gas result

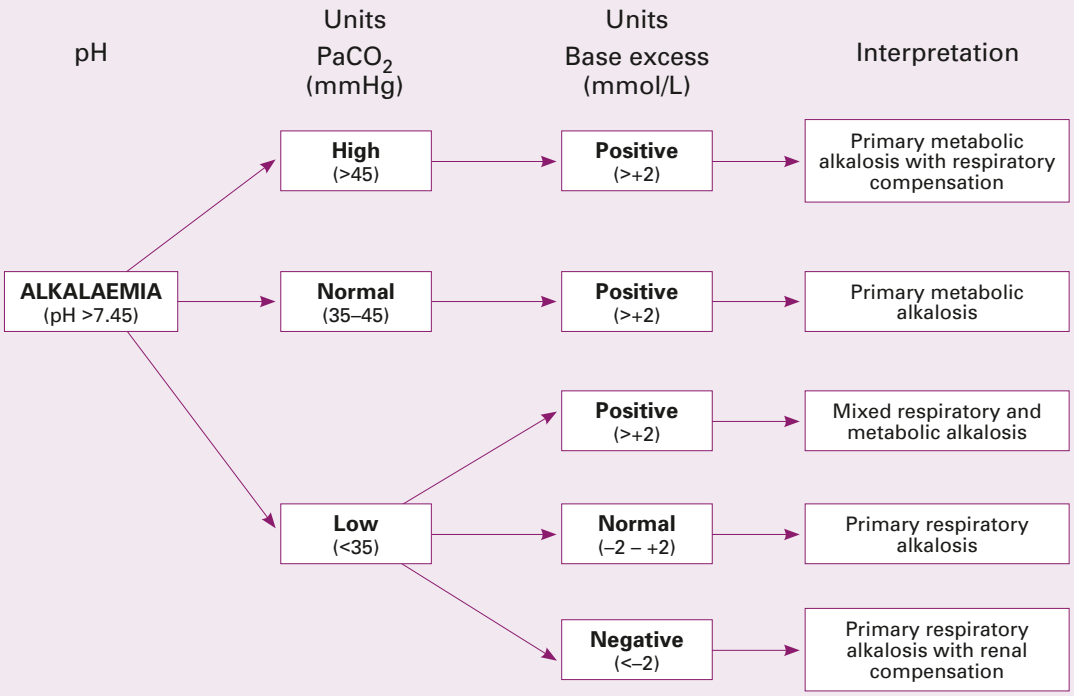

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Fig. 2 and Fig. 3 are algorithms for the consideration of primary and mixed acid–base disorders.[4]

Limitations of blood gas analysis

The blood gas analysis cannot yield a specific diagnosis. A patient with asthma may have similar values to another patient with pneumonia. Alternatively, a patient with chronic obstructive pulmonary disease and respiratory failure may have similar results to a patient with pulmonary oedema.

The analysis does not reflect the degree to which an abnormality actually affects a patient. A low PaO_2 does not necessarily indicate tissue hypoxia, nor does a normal PaO_2 indicate adequate tissue oxygenation. Oxygen utilisation is influenced by other factors such as regional blood flow, haemoglobin affinity for oxygen and cardiac output.

Blood gas analysis cannot be used as a screening test for early pulmonary disease. Severe disease may be present before significant changes are seen in blood gases.

Venous blood gases

It is easier to obtain a venous sample than an arterial sample. In some situations analysis of venous blood can provide enough information to assist in clinical decisions. In general, the pH, CO_2 and HCO_3^- values are similar in venous and arterial blood (Box 1). The main difference is the partial pressure of oxygen in venous blood is less than half that of arterial blood. Venous blood should not therefore be used to assess oxygenation.

Conclusion

Measuring arterial blood gases can be a useful adjunct to the assessment of patients with either acute or chronic diseases. The results show if the patient is acidaemic or alkalaemic and whether the cause is likely to have a respiratory or metabolic component. The $PaCO_2$ reflects alveolar ventilation and the PaO_2 reflects the oxygenation of arterial blood. When combined with a patient's clinical features, blood gas analysis can facilitate diagnosis and management.

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Further reading

Martin L. All you really need to know to interpret arterial blood gases. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 131)

7. The partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is inversely related to alveolar ventilation.
8. The partial pressure of oxygen in arterial blood (PaO_2) reflects the gas exchange function of the lungs.

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.

Certolizumab

Cimzia (UCB)

pre-filled syringe containing 200 mg in 1 mL of liquid

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2.1

Certolizumab, like adalimumab, etanercept and infliximab, is a tumour necrosis factor inhibitor indicated for rheumatoid arthritis. It is a recombinant humanised antibody Fab' fragment which has been pegylated to extend its plasma half-life to that of the whole antibody.

Peak plasma concentrations are reached between 54 and 171 hours after subcutaneous administration and its bioavailability is approximately 80%. The terminal elimination half-life is around 14 days. However, the presence of antibodies to certolizumab increases its clearance and appears to correlate with reduced patient responses. Giving methotrexate concomitantly with certolizumab reduces the formation of anti-certolizumab antibodies.

Certolizumab is indicated for adults with moderate to severely active rheumatoid arthritis. It should be combined with methotrexate in patients who have had an inadequate response to or are intolerant to other treatments with one or more disease-modifying antirheumatic drugs. Certolizumab should only be given on its own if methotrexate is contraindicated or not tolerated.

The efficacy of certolizumab has been studied in three placebo-controlled phase III trials. One of the studies was in 982 patients with active rheumatoid arthritis who had not responded to methotrexate therapy alone. Fortnightly certolizumab (three initial 400 mg doses followed by a maintenance dose of 200 mg or 400 mg given subcutaneously) or placebo was added to methotrexate treatment. (For this trial, certolizumab was reconstituted from lyophilised powder.) Patients' response to therapy was measured over 52 weeks according to the American College of Rheumatology 20% (ACR20) criteria for improvement. This is a composite outcome based on 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. Joint damage was also assessed by radiology using a modified Sharp score.[1]

Certolizumab significantly reduced the signs and symptoms of rheumatoid arthritis compared to placebo. After 24 weeks, 58.8% and 60.8% of patients receiving 200 mg and 400 mg of certolizumab had an ACR20 response compared to 13.6% in the placebo group. Progression of joint damage was significantly less with certolizumab than with placebo – at week 52, mean changes in the Sharp score from baseline were 0.4 units for certolizumab 200 mg, 0.2 units for certolizumab 400 mg and 2.8 units with placebo. The higher certolizumab dose did not seem to offer any additional clinical benefit over the lower dose.[1]

In the trial, adverse events were comparable between groups with headache, hypertension and back pain being the most common non-infectious events. However, headache was more common with placebo (12% of patients) and hypertension was more common with certolizumab (9.2% of patients). Seven patients died while receiving treatment – one in the placebo group (cardiac arrest) and six in the certolizumab groups (hepatic neoplasm and cardiac arrest with 200 mg dose and stroke, cardiac arrest, atrial fibrillation and fatigue, and myocardial necrosis with 400 mg dose). Twelve patients receiving certolizumab withdrew because of infection. There were no withdrawals due to infection in the placebo group. Serious infections included lower respiratory tract infections, gastroenteritis, urinary tract infections and tuberculosis. Malignancies were found in 12 patients – 1/199 receiving placebo and 11/781 receiving certolizumab. At week 52, 6.4% of patients receiving certolizumab had antibodies to the study drug.[1]

Another phase III trial (619 patients) with a similar design, but using liquid certolizumab, showed similar rates of efficacy in rheumatoid arthritis after 24 weeks of treatment (ACR20 rates: 57–58% with certolizumab vs 9% with placebo). Serious infections occurred with certolizumab but not with placebo (3.2% and 2.4% of patients receiving certolizumab 200 mg and 400 mg vs 0% receiving placebo). Infections included tuberculosis, gastroenteritis, skin infections, postoperative wound infection, tooth abscess, urosepsis, pneumonia, upper respiratory tract infection and sinusitis. There was one case of lupus erythematosus rash with certolizumab 200 mg.[2]

Certolizumab without methotrexate has been assessed in a trial of 220 patients who received either certolizumab 400 mg or placebo every four weeks. After 24 weeks, 45.5% of patients receiving monotherapy had responded (ACR20) compared to only 9.3% of patients receiving placebo. Adverse effects were seen in 75.6% (84 of 111) of the people in the certolizumab group versus 57.8% (63 of 109) in the placebo group. These were mostly mild or moderate but there were three serious events with placebo (vomiting, chronic renal failure, pneumonitis) and eight with certolizumab (aggravated rheumatoid arthritis (two cases), bacterial arthritis, mastitis, benign parathyroid tumour, postural dizziness, ischaemic stroke and uterine bleeding).[3]

An open-label extension study in 402 patients indicated that the benefits of certolizumab (with or without methotrexate) may not be sustained over prolonged periods (up to 112 weeks) in some people. The presence of anti-certolizumab antibodies seemed to reduce the likelihood of maintaining a response to treatment.

As certolizumab modulates the immune system there is a risk of serious infection. It is contraindicated in active tuberculosis and other serious infections such as sepsis or opportunistic infections. Patients should be tested for active or latent tuberculosis before and during treatment. Reactivation of hepatitis B virus has been reported with certolizumab so carriers should be closely monitored for active infection. Once treatment is stopped, elimination of certolizumab may take five months, so monitoring should be continued for this period. Caution is also urged when considering certolizumab for patients with a history of cancer or demyelinating disorders.

This drug is contraindicated in patients with moderate to severe congestive heart failure. It should not be used in combination with anakinra or abatacept. Live or attenuated vaccines should not be given with certolizumab and it should not be used in pregnancy.

Certolizumab offers an alternative to patients who have not responded to other rheumatoid arthritis treatments. About two-thirds of patients in the trials responded to certolizumab when it was added to methotrexate.[1,2] Certolizumab also showed some efficacy when given as a monotherapy although response rates were 10–20% lower without methotrexate. It is not known how certolizumab will compare to the other tumour necrosis factor inhibitors as there have been no comparative trials so far.

T T manufacturer provided additional useful information

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

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

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/pmeds/auspar.htm)

Corrections

New drugs: Nebivolol (Aust Prescr 2010;33:55–6)

Following receipt of correspondence, which is published on pages 101–2 in this issue, the New drug comment on nebivolol has been corrected as follows.

In paragraph 6 the third sentence has been deleted ('This was a *post hoc* analysis … different doses of nebivolol.')

Also in paragraph 6, the fifth sentence ('The target dose … compared to placebo.') has been corrected to 'The target dose was reached by two-thirds of the patients in the nebivolol group. Nebivolol was associated with a significant reduction (absolute risk reduction of 4.2%) in the composite end point of all-cause mortality or hospitalisation (due to a cardiovascular event), compared to placebo.'

Reference 5 has been replaced by

5. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al.; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215-25.

New drugs: Miglustat (Aust Prescr 2010;33:92–3)

Paragraph 4 should start 'Regular intravenous infusion of recombinant glucocerebrosidase ...'.

Self-test questions (Aust Prescr 2010;33:84–7)

Questions 1 and 2 on page 87 should be 3 and 4.

Answers to self-test questions

1. False	3. False	5. True	7. True
2. False	4. False	6. True	8. True

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