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EDITORIAL

Clinical role of cerebrovascular imaging

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Index words: ultrasound, magnetic resonance angiography, stroke.

(Aust Prescr 2001;24:134)

Stroke is the third commonest cause of death[1] and a major contributor to long-term disability in Australia. Until about 20 years ago, our ability to investigate patients with stroke was limited. Since then there have been remarkable advances in the development of non-invasive cerebrovascular neuroimaging. The two most important techniques are, undoubtedly, magnetic resonance imaging and ultrasound.

Transcranial doppler ultrasound is cheaper and easier to apply than magnetic resonance angiography (MRA). It provides less information, but transcranial doppler can be useful as a screening tool for intracranial vessel stenoses.[2] However, the management of such stenoses is still somewhat contentious because of limited data on their natural history and the efficacy of interventions. Given this state of play, the use of transcranial doppler should be discussed with an expert in the field such as a neurologist.

MRA is much more expensive and cumbersome to use but provides much more information about a variety of intracranial pathologies. One of the most useful applications is the identification of intracranial/extracranial carotid or vertebral artery dissection – a more common cause of stroke in people under the age of 45 years than previously realised. If a general practitioner suspects this condition, because a patient complains of a sudden onset of neck or eye pain with headache (sometimes without any other neurological accompaniments), they should discuss the need for an MRA with a neurologist urgently.

The other common application of MRA is quantifying the degree of extracranial carotid artery stenosis. Bearing in mind that MRA tends to overestimate the degree of carotid stenosis[3], the degree of stenosis can be established with reasonable precision if the results of duplex ultrasound of the carotid arteries are also taken into consideration. In many centres the need for digital subtraction angiography is obviated[4] and carotid endarterectomy is performed on the basis of the information supplied by MRA and duplex ultrasound.

The methods used to screen patients at risk of stroke are advancing rapidly. The use of these two non-invasive techniques is very much part of this dynamic phenomenon. Technological advances are likely to further reduce the need for invasive investigations such as angiography.

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Conflict of interest: none declared

In this issue...

This issue explores the intricacies of the cerebral circulation using ultrasound and magnetic resonance angiography. In another first for *Australian Prescriber* some of the scans can be viewed in the electronic version of the journal.

While we are often impressed by new technology everyday practice is usually dominated by common conditions. Peter Gibson updates us on the management of chronic obstructive pulmonary disease, and Grant Townsend and colleagues advise us how to deal with common dental problems.

Just because a condition is common does not mean it needs drug treatment. Noel Cranswick points out that many medicines given to children have few proven benefits. Although there are hundreds of paediatric preparations which can be purchased without a prescription, they are not necessarily free of harmful effects.

Message to all 2001 graduates in medicine, pharmacy and dentistry

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Letters

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Combination products

Editor, – We refer to the article 'Combination products – love them or loathe them?' (Aust Prescr 2001;24:127-9) and comment on the unrealised potential of this type of agent in treating medical syndromes. Polypharmacy is a chief cause of poor compliance.[1] The recent trend for evidence-based medicine supports the use of multi-drug regimens. This is exemplified by heart failure, in which angiotensin-converting enzyme inhibitors[2], beta blockers[3] and spironolactone[4] have all been shown to improve mortality. In addition, diuretics ameliorate symptoms[5], and digoxin reduces hospital admissions.[6] Heart failure thus demands a pharmaceutical quintet, even before addressing the cause of the cardiac dysfunction. We believe that the true niche for combination products is in the management of medical syndromes, such as heart failure or the metabolic syndrome, rather than in specific risk factor control. In this context the arguments against combination therapies, as outlined in the article, are less persuasive. The doses may still need to be initially adjusted, but the stable dose will depend upon the evidence from the trials. A starter pack with graded dosages may ease initial concerns and allow manipulation of certain dose sensitive components. There would not be 'unnecessary risk' as all the components would be of proven benefit. The differing pharmacokinetics of the components would, however, still need consideration. Validation would require randomised trials comparing the combination product to the individual drugs, on an intention-to-treat basis. These combinations, rather than promoting 'lazy prescribing' would help doctors to ensure the best, evidence-based care for patients with complex problems.

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Associate Professor Robert Moulds, author of 'Combination products – love them or loathe them?', comments:

Editor, – Dr Phillips and Dr Worthley have raised an interesting point. However, it is not necessarily correct to assume that because ACE inhibitors, beta blockers and spironolactone have each individually been shown to improve mortality in heart failure, then all, or even most, patients should be treated with all three drugs. Similarly, trials which show digoxin reduces hospital admissions do not mean all patients should be treated with digoxin. Each of the sets of trials studying those drugs had significant (and different) inclusion and exclusion criteria, and the results cannot necessarily be extrapolated to all patients with heart failure. Indeed it would be an interesting exercise to look at a series of patients with heart failure and see how many would have met the entry criteria, and would have had no exclusion criteria, for each of the trials showing the benefits of ACE inhibitors, beta blockers, spironolactone and digoxin. My guess is relatively few patients would qualify.

There would also be difficulty in finding kinetically suitable combinations, and difficulty with the initial dose titration required with some of the drugs, not to mention finding a pharmaceutical company with deep enough pockets to sponsor the clinical trials necessary to establish that a combined heart failure tablet is equally as efficacious as the individual components.

Despite the seeming attraction, I doubt we will see a combination treatment for heart failure in the near future.

Managing warfarin therapy in the community

Editor, – In the article 'Managing warfarin therapy in the community' (Aust Prescr 2001;24:86–9) the authors state that there is good evidence that warfarin therapy is indicated for patients more than 50 years old who have non-valvular atrial fibrillation. This implies that almost all patients with non-valvular atrial fibrillation – including those with and without risk factors for stroke such as previous cerebrovascular events, structural heart disease, significant left ventricular systolic dysfunction, hypertension, left ventricular hypertrophy and diabetes – warrant anticoagulation with warfarin. The Framingham experience[1] would suggest that only about 5% of all patients with non-valvular atrial fibrillation are less than 50 years old.

The American College of Chest Physicians Consensus Conference on anti-thrombotic therapy[2] suggests that there is no need to consider warfarin in patients under the age of 65 years in the absence of risk factors for stroke. There is uncertainty about the risk faced by those with non-valvular atrial fibrillation including women up to the age of 75 years and men of any age. The 65–75 year age range includes a substantial proportion (approximately 20%) of the patients with non-valvular atrial fibrillation.

More recent data from a study[3] of more than 1700 American Medicare beneficiaries (aged 65–95 years and clearly a sicker population than patients in previous anticoagulant trials) supported the view that in the absence of risk factors anticoagulant therapy could not be strongly recommended before the age of 75 years in either males or females.

It is therefore important for the clinician to try and assess the benefits of anticoagulation based on the risk of ischaemic and especially disabling stroke in the patient with non-valvular atrial fibrillation. Unfortunately debate on the age factor is undermined by the difficulties of managing warfarin in practice and by the lack of prospective trial data on patients randomly anticoagulated according to age cohorts.

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Professor Alex Gallus, one of the authors of 'Managing warfarin therapy in the community', comments:

Dr Hale's comments are correct and we cannot better his reading of the literature. The decision to start preventive treatment with warfarin in atrial fibrillation is a serious one. Apart from the immediate inconvenience it commits a patient who may be otherwise well to a lifelong increase in bleeding risk. Therefore, before starting warfarin in any individual with atrial fibrillation, the risks of systemic embolism without therapy and of bleeding due to therapy must be formally assessed, recorded and balanced. We had not intended our Table 1 to suggest that all patients with atrial fibrillation need warfarin if they are more than 50 years old. The American College of Chest Physicians Consensus Conference provides useful information. There were detailed discussions on the indications for warfarin in atrial fibrillation[1], and about patient related risk factors for bleeding during therapy.[2]

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Top 10 drugs

These tables show the top 10 subsidised drugs in 2000-01. The tables do not include private prescriptions.

Table 1

Top 10 drugs by defined daily dose/thousand population/day*

Drug	*PBS/RPBS †*
1. atorvastatin	52.814
2. simvastatin	38.596
3. celecoxib	34.527
4. salbutamol	26.452
5. frusemide	23.797
6. ranitidine hydrochloride	19.891
7. ipratropium bromide	18.479
8. omeprazole	18.229
9. amlodipine besylate	17.992
10. irbesartan	17.366

Table 2

Top 10 drugs by prescription counts

Drug	*PBS/RPBS †*
1. simvastatin	4,785,785
2. paracetamol	4,752,399
3. atorvastatin	4,745,607
4. celecoxib	3,850,569
5. ranitidine hydrochloride	3,790,947
6. salbutamol	3,588,326
7. codeine with paracetamol	3,015,979
8. temazepam	2,837,752
9. omeprazole	2,761,884
10. atenolol	2,646,123

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

Table 3

Top 10 drugs by cost to government

Drug	*PBS/RPBS † DDD/1000/day*	*PBS/RPBS scripts*	*Cost to government ($A)*
1. simvastatin	38.596	4,785,785	284,848,016
2. atorvastatin	52.814	4,745,607	279,681,834
3. celecoxib	34.527	3,850,569	210,259,889
4. omeprazole	18.229	2,761,884	198,064,392
5. olanzapine	2.557	507,167	112,921,245
6. pravastatin	10.202	1,473,711	87,904,278
7. sertraline	16.989	2,256,615	87,259,122
8. ranitidine hydrochloride	19.891	3,790,947	85,803,001
9. insulin (human)	11.426	421,974	78,922,474
10. bupropion	3.005	297,662	74,852,706

† PBS Pharmaceutical Benefits Scheme RPBS Repatriation Pharmaceutical Benefits Scheme

DIAGNOSTIC TESTS

Transcranial ultrasound – clinical applications in cerebral ischaemia

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SYNOPSIS

Transcranial ultrasound can rapidly and non-invasively image blood flow in the major basal intracranial arteries. Its accuracy makes it acceptable for use in screening for haemodynamically significant intracranial stenoses or vessel occlusions. Although it has a relatively limited field of view and is not technically feasible in approximately 10% of cases, the information obtained is becoming increasingly relevant to therapeutic decision-making in the prevention and management of stroke. Transcranial Doppler ultrasound or transcranial colour-coded duplex have the advantages of relatively low cost, ease of repeatability, and excellent safety and tolerability, but they provide inferior spatial and anatomical detail in comparison to angiographic techniques.

Index words: stroke, magnetic resonance angiography, angiography.

(Aust Prescr 2001;24:137–40)

Introduction

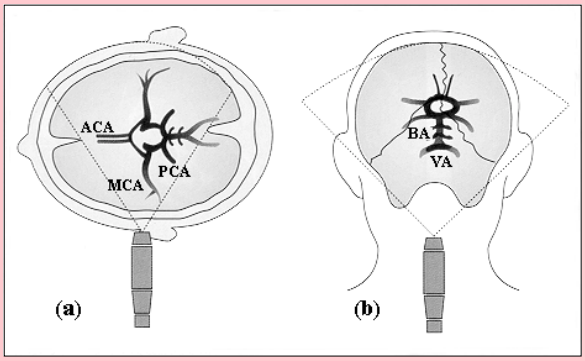
Every year approximately 40 000 Australians have a stroke and by 2020 the number of cases is expected to rise by 60%.[1] Stroke is a heterogeneous disorder with many clinical manifestations and aetiologies. The most common cause is occlusion of a large artery, resulting from or associated with thrombosis and/or artery-to-artery embolism.[2] Angiographic and sonographic imaging of intracranial vessels within six hours of the onset of an ischaemic stroke shows large artery occlusion in up to 70% of patients.[3,4] These occlusions are most commonly caused by emboli and suggest one or more sources in a proximal large artery, the aorta or the heart. In up to 66% of these patients the likely embolic source is atheromatous disease of the extracranial or intracranial carotid arteries, vertebral arteries, basilar artery or middle cerebral arteries. Approximately 5-8% of clinically relevant large artery disease in the anterior circulation (carotid, middle cerebral and anterior cerebral arteries) is located intracranially.[2] This increases to approximately 30% in the posterior circulation (vertebro-basilar/posterior cerebral arteries).[2,5] Although intracranial large artery occlusive disease is a considerably less common cause of artery-to-artery embolism than extracranial disease in the Caucasian population, the absence of a defined embolic source in the extracranial vessels or the heart should prompt evaluation of the intracranial vessels.

Transcranial ultrasound (Fig. 1)

The use of Doppler ultrasound to view intracranial basal artery blood flow was first described in 1982.[6] Subsequent advances in ultrasound technology have seen the use of combination Doppler blood flow imaging and B mode tissue imaging, so-called transcranial colour-coded duplex.[7] This more precisely identifies vessels and, if required, the direction of flow. Doppler beam angle correction gives a more accurate estimate of blood flow velocity in areas of arterial tortuosity.

Fig. 1

Schematic image of the sectional planes for the temporal and foramen magnum acoustic windows



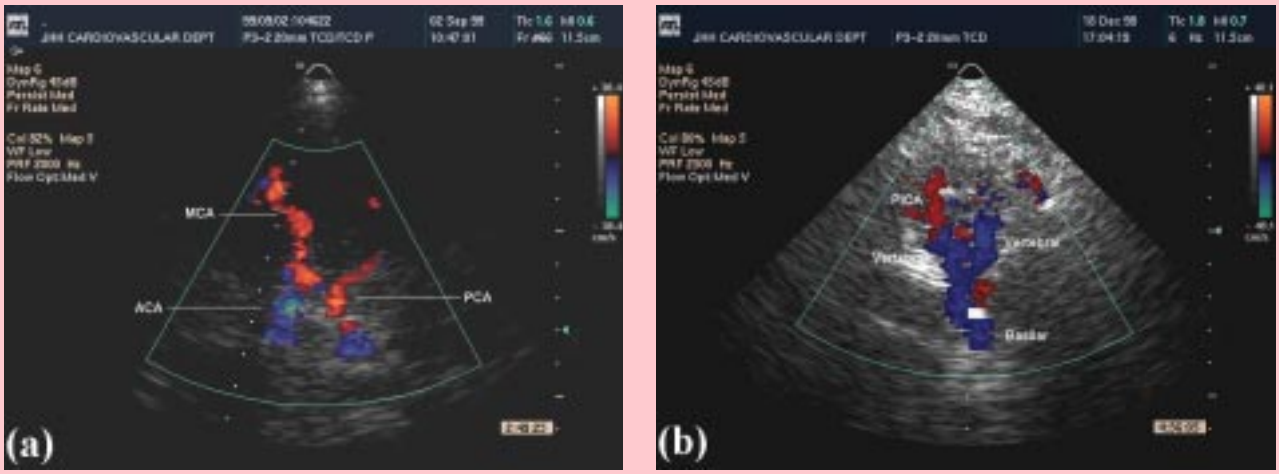
The middle cerebral artery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA) are imaged via the temporal window (a). The intracranial vertebral arteries (VA) and the basilar artery (BA) are imaged via the foramen magnum window (b).

From Bartels E. Makropathologie. Color-Coded Duplex Ultrasonography of the Cerebral Vessels. Stuttgart, New York: Schattauer 1999.

Fig. 2

Colour-coded duplex scanning of normal intracranial vessels

Images are best seen in the web (HTML) version of this article



Flow direction is colour coded with flow directed towards the transducer coded red, and flow away coded blue. Velocity is colour coded within the red/blue spectrum. Regions of focal velocity increase show as brighter zones.

(a) Segments of Circle of Willis in one cerebral hemisphere as imaged via the temporal acoustic window. This window shows the M1 and M2 segments of the middle cerebral artery (MCA), the P1 and P2 segments of the posterior cerebral artery (PCA) and the A1 segment of the anterior cerebral artery (ACA).

(b) Intracranial vertebral arteries and basilar artery to the mid portion as imaged via the foramen magnum acoustic window. The distal one-third of basilar insonation is often limited and identification of anterior and posterior inferior cerebellar arteries (PICA) is variable.

Transcranial Doppler ultrasound, and more recently transcranial colour-coded duplex, have been used for a variety of clinical purposes:

- screening for vasospasm following subarachnoid haemorrhage
- screening for intracranial vessel stenoses and occlusions in ischaemic stroke or transient cerebral ischaemia
- monitoring changes in intracranial haemodynamics and monitoring for emboli during carotid endarterectomy
- monitoring cerebral perfusion in the neurological intensive care setting.

Examples of transcranial colour-coded duplex studies of a normal circle of Willis and a normal intracranial vertebrobasilar system are shown in Figure 2. Figure 3 shows an example of a flow map and Doppler spectrum imaged in a patient with stenosis of the anterior cerebral artery.

When considering the use of transcranial Doppler ultrasound or transcranial colour-coded duplex as a screening test for occlusive disease in large intracranial arteries, the following issues need to be considered:

- accuracy – sensitivity and specificity
- feasibility – safety and tolerability, availability, cost-effectiveness
- reliability – intra- and interobserver variability in scanning and reporting.

Accuracy

Both transcranial Doppler ultrasound and transcranial colour-coded duplex provide a relatively limited view of the basal cerebral arteries (Fig. 1). The vessels that are visible on transcranial Doppler ultrasound do, however, comprise the more common sites for the development of intracranial large artery occlusive disease. It is also important to appreciate that finding a stenosis using Doppler depends on the detection of a haemodynamic disturbance of sufficient significance to produce an unequivocal elevation in blood flow velocity. In general, this requires the presence of a diameter narrowing of approximately 50% or more (equivalent to a cross-sectional area narrowing of approximately ≥75%). Although somewhat arbitrary, these cut-offs are of clinical relevance as it is not until diameter narrowing exceeds 50% that reduction in blood flow occurs. Studies of the accuracy of transcranial Doppler ultrasound or transcranial colour-coded duplex have tended, therefore, to use 50% or greater diameter narrowing as the threshold of abnormality.

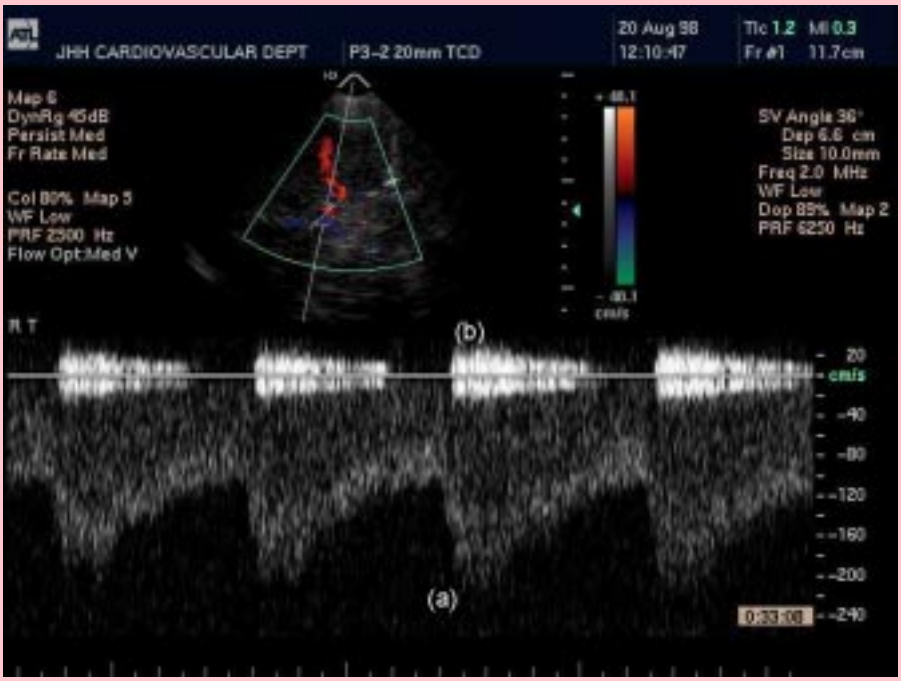
The accuracy of both transcranial Doppler ultrasound and transcranial colour-coded duplex in the detection of intracranial stenoses or occlusions has been investigated in a number of comparative studies. However, there are relatively few studies assessing the accuracy of transcranial colour-coded duplex. More recently, a number of smaller studies have found that advances in instrumentation and the use of echo-enhancing agents can improve image quality and the imaging of vessel segments that are poorly seen with standard techniques.[8,9] These advances are likely to result in improvements in both the feasibility and accuracy of transcranial colour-coded duplex.

In general, the accuracy of transcranial Doppler ultrasound and transcranial colour-coded duplex in the detection of intracranial occlusive disease can be considered acceptable

Fig. 3

Colour flow map and pulse wave Doppler spectrum of a stenosis

Images are best seen in the web (HTML) version of this article



Colour-coded duplex scanning via the right temporal acoustic window shows a focal region of increase in colour intensity in the A1 section of the anterior cerebral artery. This is accompanied by an increase in (a) flow velocity (peak systolic velocity 224 cm/sec), and (b) turbulence (high intensity, low velocity signals). Other general criteria for haemodynamically significant stenoses include circumscribed local increase in flow velocity, and left/right difference in flow velocity (in the above example, left ACA peak systolic velocity was 86 cm/sec).

when performed as 'opportunistic' screening by sonographers and clinicians experienced in its use.

Comparison with angiography

When compared to contrast angiography, transcranial Doppler ultrasound accuracy varies with the technical difficulty typically encountered in imaging any particular segment. The middle cerebral artery stem (M1 segment) is relatively easy to study, so ultrasound has a sensitivity and specificity of 90–99% for finding a stenosis or an occlusion.[10] For the more difficult to image intracranial (V4) segment of the vertebral arteries and the basilar artery, ultrasound has a sensitivity of 70–80% and a specificity of 90–99%.[10,11]

The accuracy of transcranial colour-coded duplex ultrasound is similar to that of contrast angiography. In a study of 310 patients, transcranial colour-coded duplex correctly identified 31 who had a stenosis of 50% or greater (confirmed by digital subtraction X-ray angiography).[12] As all the stenoses were correctly diagnosed as true positives the sensitivity is 100%, but the specificity is 99% because one artery with a stenosis of less than 50% was incorrectly classified as having a stenosis of more than 50% (false positive).

Comparison with magnetic resonance angiography (MRA)

Intracranial MRA has a reasonable accuracy in comparison to contrast angiography for intracranial stenoses.[13] The studies to date also suggest a good correlation between MRA and transcranial colour-coded duplex for imaging a stenosis or occlusion. In the anterior circulation arterial segments, transcranial colour-coded duplex has an estimated sensitivity of 75% and specificity of 99%, while in the posterior circulation, the sensitivity is 88% and the specificity 99%.[14]

Feasibility

The main limitation of transcranial ultrasound is the inadequacy of the acoustic window through either the temporal bone or the foramen magnum. The temporal window is more likely to be inadequate for ultrasound in women and the elderly. Up to 10% of patients undergoing transcranial Doppler ultrasound and up to 20% undergoing transcranial colour-coded duplex have inadequate acoustic windows for an optimal study. These proportions can be reduced to less than 5% with the use of intravenous transpulmonary echo-contrast drugs, however, these drugs increase the complexity and cost of the investigation.

Transcranial Doppler ultrasound and transcranial colour-coded duplex have no recognised adverse effects, a potential advantage over X-ray angiography which carries a risk of contrast allergy and stroke[15], or computerised tomographic angiography that uses ionizing radiation and also requires intravenous contrast media. The ultrasound studies are well tolerated, a potential advantage over MRA which sometimes triggers claustrophobia, necessitating the use of intravenous sedation.

Transcranial Doppler ultrasound and transcranial colour-coded duplex cost less than angiography, and the portability of the equipment allows the examination to be performed at the patients' bedside and at repeated intervals if necessary.

Studies assessing the cost-effectiveness of transcranial Doppler ultrasound or transcranial colour-coded duplex in cerebrovascular disease have not been reported.

Reliability

One of the potential limitations in all diagnostic vascular ultrasound is that a high level of technical and procedural skill is required to obtain the best quality images. In addition, a clear understanding of the clinical question being asked often enhances the detail obtained by the sonographer. Both these issues are particularly pertinent to transcranial ultrasound. While there are established criteria[16] for the diagnosis of intracranial stenoses and occlusion using either transcranial Doppler ultrasound or transcranial colour-coded duplex, there are few studies evaluating intra- or interobserver variations in reporting.

Imaging influences management

Advances in brain imaging techniques now allow therapeutic decisions about the acute management and prevention of stroke to be made with a detailed understanding of the nature and severity of the underlying arterial pathology.[17] For example, in intracranial occlusive disease, the finding of a middle cerebral artery or basilar artery occlusion in a patient with an acute stroke, is an indication for the use of thrombolytic therapy (in appropriately resourced centres).[18,19] Conversely, the finding of a high grade intracranial stenosis in the artery supplying a recently ischaemic region of the brain, should prompt the clinician to consider prescribing anticoagulation rather than antiplatelet therapy for secondary prevention, as present evidence suggests anticoagulation has a therapeutic advantage. Without imaging to assess the arterial pathology, the most appropriate evidence-based intervention cannot be identified.

Conclusion

The major clinical application of transcranial ultrasound is as a specific investigation for intracranial occlusive disease when used in conjunction with ultrasonic studies of the extracranial cerebral vasculature and computerised tomographic scanning of the brain. This information can be used to guide the choice of treatment for preventing and managing strokes. Advances in instrumentation and the application of echo-contrast drugs are likely to improve the accuracy and reliability of transcranial ultrasound techniques.

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NOTE

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 158)

1. Patients with an allergy to contrast media should not have colour-coded duplex scanning.
2. Occlusions of large cerebral arteries are usually caused by emboli from elsewhere in the vascular system.

Magnetic resonance angiography of the cerebrovascular system

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SYNOPSIS

Arterial blood flow is not shown clearly by magnetic resonance imaging, but it can be revealed by magnetic resonance angiography. This technique manipulates the signal from blood so that the vessels are distinguished from the surrounding tissues. Magnetic resonance angiography can be used to detect intracranial aneurysms, intracranial vascular disease and thrombosis of the major cerebral veins. It is the investigation of choice if dissection of the carotid or vertebral artery is suspected. Although new techniques can produce images quickly, magnetic resonance angiography is unsuitable for patients who cannot lie motionless inside the scanner until the image is acquired, or who have contraindications to having magnetic resonance imaging.

Index words: aneurysm, atherosclerosis, arterial dissection, stroke.

(Aust Prescr 2001;24:141–3)

Introduction

Magnetic resonance angiography (MRA) is a magnetic resonance imaging (MRI) technique which can distinguish vascular flow from the surrounding tissues. It is now in routine use as a non-invasive tool for imaging the cerebral vasculature. In cerebrovascular disease it is the investigation of choice for patients who are suspected of having:

- unruptured intracranial aneurysms
- intracranial vascular disease associated with acute infarction
- transient ischaemic attacks (TIA) (not all patients require imaging)
- intracranial and/or extracranial dissection of the carotid and/or vertebral arteries
- thrombosis of major cerebral veins and dural venous sinuses.

MRA may also be helpful as part of the initial investigation of patients with suspected intracranial vasculopathies related to a variety of other disorders such as pre-eclampsia/eclampsia, vasculitis, neurofibromatosis, radiation therapy, intracranial infection, and cerebral vascular malformations.

Advances in MR surface coil technology as well as the use of intravenous contrast media have now made it possible to obtain an angiographic study of the cervical and intracranial vessels in a single breath-hold.

Magnetic resonance angiography techniques

All the images are produced using either a time-of-flight (TOF) or phase-contrast technique. The TOF technique takes less time and is more commonly used. It is based on the principle that flowing protons entering a slice of tissue possess full longitudinal magnetisation and therefore high signal intensity. By suppressing the signal from the surrounding tissue, the technique highlights vessels with flowing blood. Phase-contrast techniques utilise velocity differences and phase shifts in moving blood to provide image contrast. This can be used to assess the speed and direction of the blood flow. Both techniques are capable of two- or three-dimensional imaging depending upon whether individual slices or volumes of tissue are excited by the radiofrequency pulse. Reconstruction of the images results in most of the signal from the surrounding soft tissues being removed, allowing the vessels to be visualised in greater detail. Three-dimensional TOF MRA is the technique which is most often used for evaluating the intracranial arteries and veins. Some centres use phase-contrast MRA when imaging the cerebral venous system.

Three-dimensional TOF MRA can be subject to artifacts which may cause misrepresentation of vessel pathology. MRA images are extremely sensitive to degradation by movement, mainly because it takes a relatively long time to acquire the image. If the patient moves or swallows at any time it can render an entire study non-diagnostic. Conventional angiography or ultrasound are preferred for patients who are unable to remain still for approximately 10 minutes.

Routine cerebral MRA does not require the use of intravenous or intra-arterial contrast agents. Intravenous contrast is being used in a new technique; three-dimensional contrast-enhanced breath-hold MRA is being increasingly used to evaluate the cervical and cranial arteries. It has a lower resolution, for the intracranial circulation, than TOF MRA, because it has a larger field of view, but it has the advantage of allowing the cervical and intracranial vessels to be imaged in the time taken for a single breath-hold. The technique is most useful for the evaluation of atherosclerotic disease involving the aortic arch and proximal cervical vessels and for other conditions affecting these vessels such as congenital anomalies and arteritides.

Cerebrovascular applications

Suspected TIA or stroke

Three-dimensional TOF MRA can be used in acute stroke. Images of the internal carotid, vertebral and basilar arteries and their major branches can be obtained in 6–8 minutes (Fig. 1). The small peripheral branches of the anterior, middle and posterior cerebral arteries are too small to be demonstrated by routine MRA.

Intracranial vessels

Irregularities in the calibre and contour of a vessel can suggest the presence of atheroma, thrombus/embolus, or vascular diseases such as fibromuscular dysplasia or vasculitis. A reduced signal within an intracranial internal carotid artery may be a sign of a critical stenosis of the cervical portion of the vessel.

Dural venous sinus thrombosis accounts for approximately 1–2% of acute strokes in young adults. Intracranial venous MRA (MR venography) provides excellent, non-invasive visualisation of the dural venous sinuses and the larger deep cerebral and cortical veins.

Extracranial vessels

Non-invasive techniques such as carotid duplex ultrasound, CT angiography and MRA are now used in preference to angiography in the investigation of suspected extracranial carotid arterial disease. Three-dimensional TOF MRA tends to overestimate the degree of stenosis compared with conventional angiography, but correlates well with the estimates obtained by duplex ultrasound. Ultrasound and MRA have a high sensitivity and specificity in estimating stenoses greater than 70%.[1]

MRA is less sensitive than ultrasound for distinguishing between severe stenosis and occlusion. Significant signal loss can occur as a result of turbulent flow near a stenosis and this can in turn lead to difficulty in differentiating between severe stenosis and complete occlusion, but this can usually be resolved with angiography.

At present, the cost and availability of ultrasound make it the investigation of choice in the patient with a suspected critical extracranial carotid stenosis, but MRA can be useful in confirming an equivocal ultrasound abnormality. MRA is the preferred test if arterial dissection is suspected.

Improvements in MRI hardware, software and coil development, as well as the use of intravenous contrast now allow the cervical vessels to be imaged in a single breath-hold.[2] Using this technique a complete study of the aortic arch and supra-aortic arteries can be performed in only a few minutes.

Dissection

Dissection of the carotid and vertebral arteries is another cause of arterial occlusion and embolism. It accounts for up to 20% of strokes in younger patients. The goal of MRA is to identify the presence and level of the dissection and to determine the impact on cerebral blood flow. MRA is nearly 100% accurate in revealing a dissection, and has a good correlation with angiography in determining the exact site of the dissection and the degree of stenosis.[3] MRI with MRA is currently the investigation of choice for suspected dissection.[4,5] Difficult cases may require further anatomical clarification with angiography.

Fig. 1

Three-dimensional time-of-flight magnetic resonance angiography of the intracranial vessels supplying and comprising the Circle of Willis

L = left R = right BA = Basilar artery MCA = Middle cerebral artery PCA = Posterior cerebral artery
ACA = Anterior cerebral artery VA = Vertebral artery CA = Internal carotid artery

Intracranial aneurysms

Rupture of an intracranial aneurysm is the commonest cause of non-traumatic subarachnoid haemorrhage. Conventional angiography is the investigation of choice for an acute subarachnoid haemorrhage confirmed by lumbar puncture or cerebral CT. This is because angiography is more sensitive than MRA in assessing the anatomy and morphology of the aneurysm, to assist the neurosurgeon or interventional neuroradiologist. Angiography is also more sensitive than MRA for aneurysms of less than 3 mm. It is better for patients who are medically unstable or unco-operative as they cannot easily be monitored, sedated and anaesthetised inside the MR scanner.

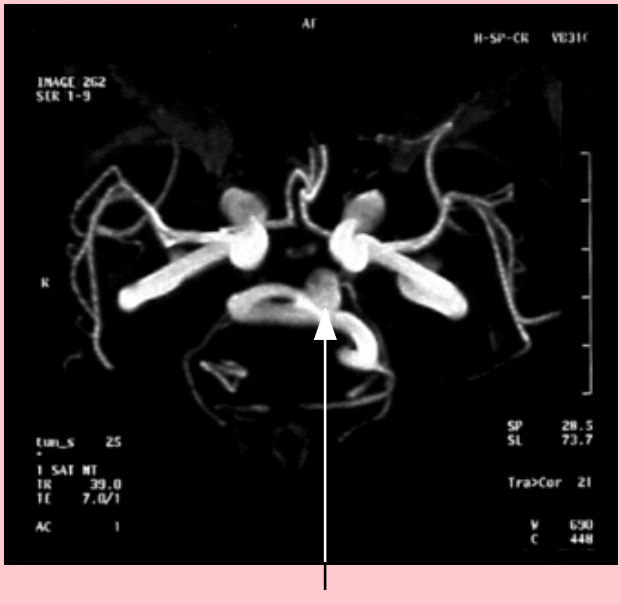
The role of MRA in screening for asymptomatic aneurysms in people at increased risk is unclear. While the prevalence of asymptomatic aneurysms in the general population is unknown, up to 15% of people with two first degree relatives who have had a subarachnoid haemorrhage will also have an aneurysm. The sensitivity of three-dimensional TOF MRA for aneurysms greater than 3 mm in size has been reported as 95% (Fig. 2). Recent studies have assessed the resource implications of screening people at risk and the theoretical reduction in morbidity and mortality. They concluded that screening would pose a logistical burden, and have major financial implications.[6] Screening currently is on a case by case basis and is not accurate enough to exclude small (less than 3 mm) aneurysms.

Vascular malformations

Although angiography is the definitive technique for evaluating arteriovenous malformations before treatment, they can be well characterised by using a combination of TOF and phase-contrast MRA. Currently, MRA is only used in conjunction with angiography.

Fig. 2

Three-dimensional time-of-flight intracranial magnetic resonance angiography which demonstrates a 6 mm aneurysm arising from the basilar artery tip and projecting anteriorly



aneurysm

Conclusion

MRA has become an essential component of MRI in the evaluation of many types of cerebrovascular disease. Further advances in hardware and software in the future will result in improved resolution of smaller vessels. MRA is likely to replace angiography for a large number of clinical applications. Angiography will be reserved mainly for unstable patients and interventional angiographic procedures.

ACKNOWLEDGEMENT

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 158)

3. Magnetic resonance angiography is an accurate method of imaging a dissection of the vertebral artery.
4. Magnetic resonance angiography has superseded angiography in the investigation of subarachnoid haemorrhage.

Management of acute dental pain: a practical approach for primary health care providers

John Wetherell, Senior Lecturer, Lindsay Richards, Associate Professor, Paul Sambrook, Senior Lecturer, and Grant Townsend, Professor of Dental Science, University of Adelaide, Adelaide

SYNOPSIS

A detailed history and examination will identify the cause of dentally-related pain in most emergency situations. Sharp, shooting pain can be caused by inflammation in the pulp or exposure of the dentine. Dull throbbing pain has several causes including ulcerative gingivitis, dental caries and food impaction. Simple treatment will usually alleviate the symptoms until patients can be seen by a dentist. Prescription of antibiotics is usually not indicated.

Index words: dental infections, sinusitis, temporomandibular joint.

(Aust Prescr 2001;24:144–8)

Introduction

General medical practitioners are often called upon to manage acute dental pain in emergency situations, for example, out of hours or in rural Australia, where it may not be possible for a dentist to provide immediate treatment. Common acute oral problems are usually easy to diagnose. Simple management can alleviate pain and further discomfort until a dentist can be called upon.

Most problems can be identified by the history and examination. Several dental conditions have typical symptoms with different types of pain.

History and examination

When investigating acute dental pain, the history should focus on the pain's:

- location
- type
- frequency and duration
- onset
- exacerbation and remission (for example the response to heat or cold)
- severity
- area of radiation.

Associated pathology and referred pain should also be considered.

The following structures need to be examined carefully in order to be sure that the pain is of dental origin:

- tongue
- buccal mucosa
- floor of the mouth
- hard palate
- teeth and periodontal tissues (see Fig. 1)
- tonsils
- temporomandibular joints
- airway
- ears
- salivary glands
- lymph nodes.

Which tests can assist in diagnosis?

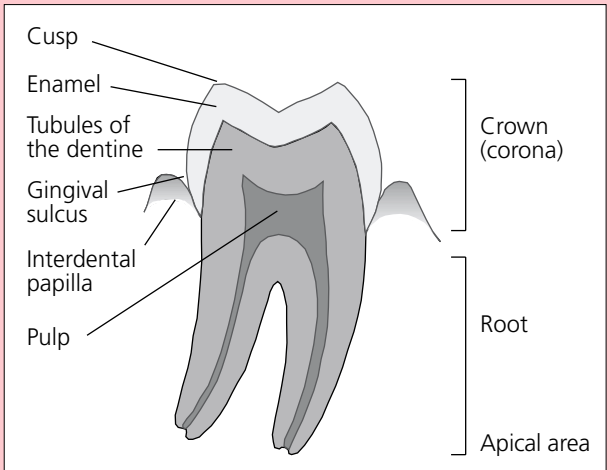
There are several simple tests that may assist in diagnosis of dental pain.

Pulp sensitivity test

Dry ice, or an ordinary ice stick (made in a plastic or glass tube), is placed on the cervical third (neck region) of the tooth crown. A response to the stimulus indicates that the pulpal tissue is capable of transmitting nerve impulses. No response may indicate pulp necrosis.

Fig. 1

Diagram of a lower molar tooth



Percussion test

Using an instrument handle, the tooth is tapped in the longitudinal axis. A painful response suggests possible periapical inflammation.

Probing

Placing a fine, blunt probe gently into the gingival sulcus surrounding the tooth enables the health of the gingival tissues to be assessed. Bleeding and/or sulcus depths greater than 3–4 mm indicate gum disease.

Mobility test

Holding a tooth firmly on the buccal (cheek) and lingual sides between the fingers enables mobility to be assessed. All teeth have a small amount of mobility (<0.5 mm), but visible movement suggests loss of bone support around the root of the tooth.

Palpation

Careful palpation around the area of concern may reveal tenderness and the type and extent of swelling.

Radiographic examination

If it is possible to obtain a screening radiograph, such as an orthopantomograph (OPG), this may assist in the diagnosis and localisation of the cause of the pain. The radiograph should show clearly the apical and periapical structures of teeth and associated tissues. The relationship of the maxillary molars and premolars to the floor of the maxillary sinus can be examined, and radiographs may reveal recurrent caries or periapical radiolucencies associated with an established infection (Fig. 2).

What are the common types of dental pain?

Common types of oro-facial pain likely to cause a patient to seek emergency care are categorised in Figure 3. The character of the pain can point to a diagnosis.

Short, sharp, shooting pain

This type of pain can be generalised or confined to one region of the mouth. The pain may be due to fluid movement through open tubules in the dentine or there may be some initial inflammatory changes in the dental pulp. It can be caused by caries, dentine exposure on root surfaces, split cusp, lost or fractured restoration or a fractured tooth.

Patients complain commonly of a sharp pain associated with hot, cold or sweet stimuli. The pain is only present when a stimulus is applied. In the case of a cracked cusp, grainy bread or hard food may create a sharp pain, that may be spasmodic, on biting or chewing.

With gingival recession, recent scaling, or tooth wear due to a high acid diet or gastric reflux, there may be generalised dentine sensitivity. However, with caries, fractured fillings and cracked cusps, the pain tends to be localised to the affected tooth.

Intermittent sharp, shooting pains are also symptomatic of trigeminal neuralgia, so care must be taken not to mistakenly label toothache as neuralgia.

Treatment

For root sensitivity the use of a desensitising toothpaste and a reduction in acid in the diet will help resolve the symptoms. The use of a fluoride mouth-rinse may also help. In the case of caries, a lost filling or fractured tooth, coverage of the

Fig. 2

An orthopantomograph (OPG) showing extensive dental caries (radiolucent areas) affecting the crowns of several teeth, and abscess formation (radiolucent areas) around the periapical regions of the roots. Arrows show caries and abscess formation on two mandibular teeth.

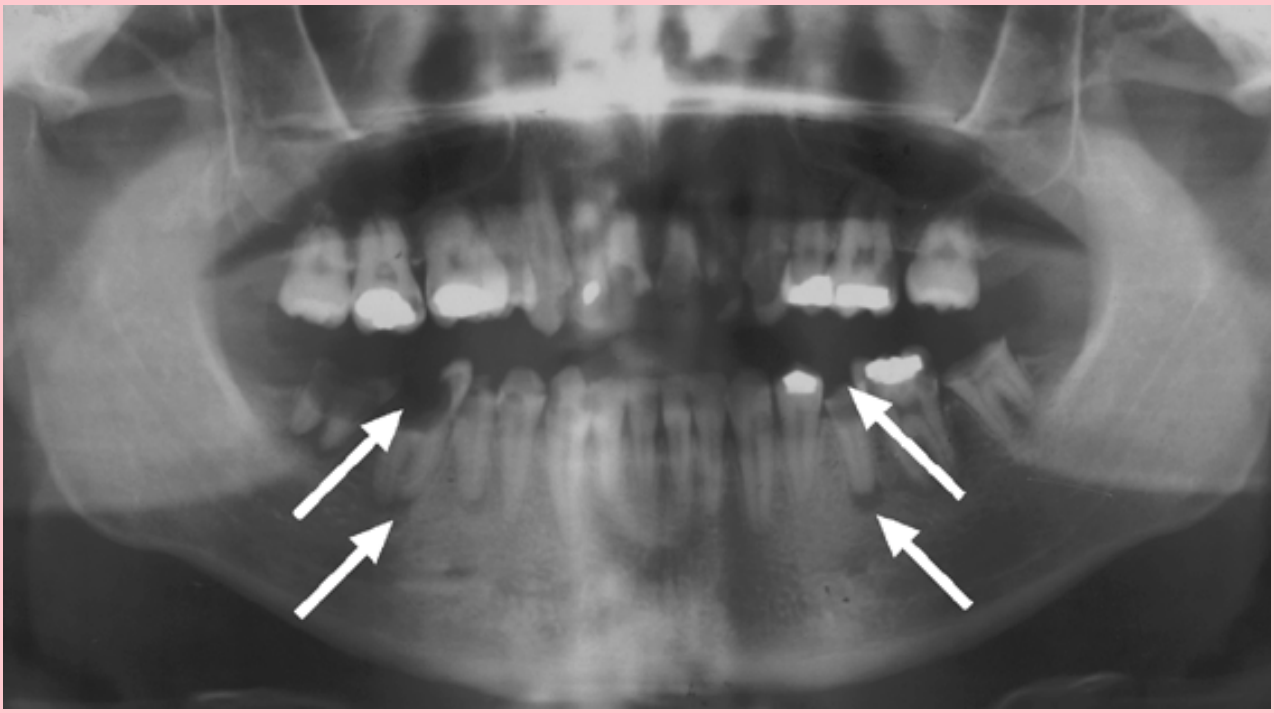
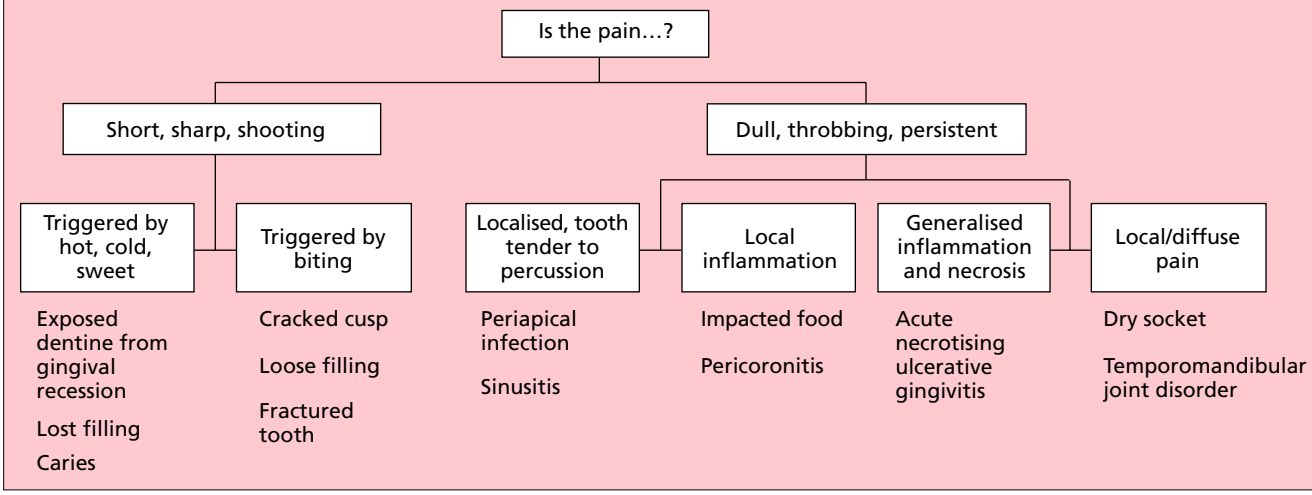


Fig. 3

Causes of common types of dental pain



exposed dentine with a temporary restoration will usually relieve the symptoms.

Dull, throbbing, persistent pain

This type of pain may have several causes. These include tooth problems, food impaction, pericoronitis, acute necrotising ulcerative gingivitis, temporomandibular disorder, or even maxillary sinusitus.

Painful tooth problems

The most common dental cause of dull, throbbing persistent pain is caries. In many cases this is recurrent and associated with an existing restoration. Where the pulp is affected irreversibly, necrosis may follow with possible development of a periapical infection. A fractured cusp involving the pulp, or a large deep restoration may also be associated with this type of pain. Affected teeth may be tender to percussion in the later stages of periapical inflammation.

There is considerable variation in the pain reported by patients, but it commonly starts as a sharp stabbing pain that becomes progressively dull and throbbing. At first the pain may be caused by a stimulus, but it then becomes spontaneous and remains for a considerable time after removal of the stimulus. The pain may radiate and be referred to other areas of the mouth. This type of pain tends to cause the patient to have difficulty sleeping and may be exacerbated by lying down. Heat may make the pain worse whereas cold may alleviate it. The pain may be intermittent with no regular pattern and may have occurred over months or years. If there is periapical infection present, patients may no longer complain of pain in response to a thermal stimulus, but rather of sensitivity on biting.

Treatment

Treatment of affected teeth will involve either root canal therapy or tooth removal. In some patients, periapical inflammation can lead to a cellulitis of the face characterised by a rapid spread of bacteria and their breakdown products into the surrounding tissues causing extensive oedema and pain. If systemic signs of infection are present, for example, fever and malaise, as well as swelling and possibly trismus (limitation of mouth opening), this is a surgical emergency. Antibiotic treatment alone is not suitable or recommended (see box). If pus is present, it needs to be drained, the cause eliminated, and host defences augmented with antibiotics. The microbial spectrum is mainly gram positive including anaerobes. Appropriate antibiotics would include a penicillin or a 'first generation' cephalosporin, combined with metronidazole in more severe cases.

Paracetamol or a non-steroidal anti-inflammatory drug is the recommended analgesic in the initial treatment of dental pain.

Food impaction and pericoronitis

Soft tissue problems that may cause dull, throbbing, persistent pain include local inflammation (acute gingivitis associated with food impaction) or pericoronitis.

Chronic periodontitis with gradual bone loss, rarely causes pain and patients may be unaware of the disorder until tooth mobility is evident. There is quite often bleeding from the gums and sometimes an unpleasant taste. This is usually a generalised condition, however, deep pocketing with extreme bone loss can occur around isolated teeth. Food impaction in

Should antibiotics be prescribed?

While antibiotics are appropriate in the management of certain dental infections, they are not indicated if the pain results from inflammatory (non-infective) or neuropathic mechanisms. The degree of pain is not a reliable indicator of acute infection.

There is evidence that Australian dentists and doctors are using antibiotics empirically for dental pain, rather than making careful diagnoses of the causes of the pain.[1] Most dental emergency situations involve patients with acute inflammation of the dental pulp or the periapical tissues. Prescribing antibiotics for these conditions will not remove the cause of the problem nor destroy the bacteria within the tooth.

Antibiotics should be limited to patients with malaise, fever, lymph node involvement, a suppressed or compromised immune system, cellulitis or a spreading infection, or a rapid onset of severe infection.

these areas can cause localised gingival pain. Poor contact between adjacent teeth and the presence of an occluding cusp forcing food into this gap can also cause a build-up of food debris and result in gingival inflammation.

Acute pericoronitis involves bacterial infection around an unerupted or partially erupted tooth and usually affects the lower third molar (wisdom tooth). The condition is often aggravated by the upper molar impacting on the swollen flap of soft tissue covering the unerupted tooth. There may be trismus.

Treatment

Food debris should be removed and drainage established, if pus is present. Irrigation with chlorhexidine and rinsing the mouth with hot salty water is recommended. Early referral to a dentist is indicated. Cellulitis can develop, requiring urgent referral to a surgeon.

Acute necrotising ulcerative gingivitis

Acute necrotising ulcerative gingivitis is a rapidly progressive infection of the gingival tissues that causes ulceration of the interdental gingival papillae. It can lead to extensive destruction. Usually young to middle-aged people with reduced resistance to infection are affected. Males are more likely to be affected than females, with stress, smoking and poor oral hygiene being predisposing factors. Halitosis, spontaneous gingival bleeding, and a 'punched-out' appearance of the interdental papillae are all important signs.

The patients quite often complain of severe gingival tenderness with pain on eating and tooth brushing. The pain is dull, deep-seated and constant. The gums can bleed spontaneously and there is also an unpleasant taste in the mouth.

Treatment

As there is an acute infection with mainly anaerobic bacteria, treatment follows surgical principles and includes superficial debridement, use of chlorhexidine mouthwashes and a course of metronidazole tablets. Treating the contributing factors should prevent a recurrence.

Dry socket

A dull throbbing pain develops two to four days after a mandibular tooth extraction. It rarely occurs in the maxilla. Smoking is a major predisposing factor as it reduces the blood supply. The tissue around the socket is very tender and white necrotic bone is exposed in the socket. Halitosis is very common.

Treatment

The area should be irrigated thoroughly with warm saline solution. If loose bone is present, local anaesthesia may be necessary to allow thorough cleaning of the socket. Patients should be shown how to irrigate the area and told to do this regularly. Analgesics are indicated, but pain may persist for several days. Although opinion is divided as to whether or not dry socket is an infective condition, we do not recommend the use of antibiotics in its management (see box).

Temporomandibular disorders

Temporomandibular disorders may lead to pain that is confused with toothache. Patients usually complain of unilateral vague pain occurring in the joint area and in the surrounding muscles of mastication. If the patient bruxes (clenches or grinds) at night, then pain in the temporal area on waking is common. Patients who clench during the day may find they get symptoms at the end of the day. The symptoms are often cyclical, resolving then recurring again. On questioning, patients will frequently be able to reveal stressful incidents that may have triggered this process. Palpation of the muscles of mastication will elicit tenderness, usually unilaterally. There may also be tenderness around the temporomandibular joints, limitation in mouth opening and obvious wear of the teeth. This wear may contribute to dentine sensitivity, as the enamel is worn away by the tooth grinding. Wear facets will be seen on restorations as well as natural teeth. Quite often, neck and shoulder muscles are tender to palpation. There may be joint pain with clicking and grating.

Treatment

Reassurance about the self-limiting nature of the problem and its reversibility may be all that is needed. Anti-inflammatory drugs and muscle relaxants can also help. Construction of a night-guard and muscle exercises may be indicated subsequently. These exercises may include gentle passive stretching, or resistance and clenching exercises.[2]

Sinusitis

This is caused by infection of the maxillary sinus, usually following an upper respiratory tract infection. However, there can be a history of recent tooth extraction leading to an oro-antral fistula. Patients usually complain of unilateral dull pain in all posterior upper teeth. All these teeth may be tender to percussion, but they will respond to a pulp sensitivity test. There are usually no other dental signs.

The pain tends to be increased on lying down or bending over. There is often a feeling of 'fullness' on the affected side. The pain is usually unilateral, dull, throbbing and continuous. Quite often the patient feels unwell generally and feverish.

Treatment

Pain originating from the sinus arises mainly from pressure. Decongestants can help sinus drainage. Antibiotics probably have only a minor role in mild cases. Referral to an otorhinolaryngologist for endoscopic sinus surgery may be indicated in chronic cases.[3]

Managing dental trauma

Avulsed tooth

Avulsed deciduous (baby) teeth are generally not reimplanted, as they may become fused to the alveolar bone and impede subsequent emergence of the permanent successor.

It is essential to reimplant permanent teeth as soon as possible. However, while the tooth is out of the alveolus it should be stored in a physiological medium, for example, normal saline, milk, or the vestibule of the mouth.

Before reimplantation, the root surface should be cleaned gently with normal saline to remove debris, but the root

should not be touched with the fingers. The tooth socket should be irrigated gently with normal saline to remove any blood clot that has formed. The tooth should then be replaced into the socket using minimal pressure, and splinted to the adjacent teeth with a flexible splint (e.g. aluminium foil, bluetack).

When a tooth is reimplanted, an antibiotic is prescribed for five days and a tetanus booster is given if immunisation is not up to date.

Fractured tooth

If the crown of a tooth is fractured by trauma and the broken fragment is available, it should be stored in a physiological medium until a dentist can assess the patient. Coverage of exposed dentine on the fractured crown with a temporary restoration is desirable to protect the underlying pulp tissue.

Placement of temporary restorations

Although it is unlikely that many general medical practitioners will have temporary filling materials available in their surgeries, dentine that has been exposed by caries, a lost filling or tooth fracture can be covered relatively easily with glass ionomer cement (GIC) or zinc oxide eugenol (ZOE) materials. Most GIC materials are dispensed in capsules but a hand-mixed material is available, consisting of a powder, liquid and conditioner. The surface of the cavity is painted with the conditioner, then rinsed and dried, before placement of the filling. Zinc oxide eugenol materials consist of a powder and liquid (oil of cloves) that are mixed to a putty-like consistency before placement in the tooth.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 158)

5. A painful dry socket is a complication of mandibular tooth extraction.
6. Penicillin V is a suitable antibiotic for treating a dental abscess once the pus has been drained.

Book review

Therapeutic Guidelines: Endocrinology. Version 2. North Melbourne: Therapeutic Guidelines Limited; 2001. 227 pages. Price (postage not included): $31.90 (2001), $33 (2002); students $25.30.

David Mills, General Practitioner, Port Lincoln, South Australia

This latest version of Therapeutic Guidelines: Endocrinology is an excellent reference source for busy general practitioners. Given the rise in many endocrine-related conditions, this is timely. The layout is simple and easy to follow with more space devoted to common conditions such as diabetes and osteoporosis, although a large number of conditions are still covered. There is a concise and succinct drug summary at the start of the book called 'Getting to know your drugs' allowing easy cross-referencing from the text. There are also some brief appendices on endocrine emergencies, pregnancy and breastfeeding, and for those interested in searching further, related web sites.

The diabetes sections are well set out and reinforce the current diagnostic criteria based on American Diabetes Association/ World Health Organization guidelines. Treatment targets are up to date as is the advice on treating difficult complications such as neuropathy. Current drug therapies are outlined logically, but some drugs such as the 'glitazones' are not available on the Pharmaceutical Benefits Scheme.

Osteoporosis is now high on the agenda of many general practitioners and this section is excellent with clear, current principles on diagnosis, prevention and management. All of the drugs described are available and well known to general practitioners, making the reading very practical.

Under the sections on contraception there is good coverage of topical issues such as depot medroxyprogesterone, the etonogestrel implant and the levonorgestrel intrauterine devices. Similarly there is a comprehensive and easy to read discussion on hormone replacement therapy addressing most of the well-known controversies.

Overall this book reads extremely well and fulfils the general practitioner's need for evidence-based guidelines, in a short but easily understood form. It compares well with other general practice guidelines such as Evidence Based Medicine.

David Mills has been in rural general practice for 15 years. He is a clinical lecturer at the Department of General Practice at the University of Adelaide and sits on the South Australian Diabetes Advisory Group.

Over-the-counter medication in children: friend or foe?

Noel Cranswick, Clinical Pharmacologist, and George McGillivray, Fellow in General Paediatrics, Royal Children's Hospital, Melbourne

SYNOPSIS

Over-the-counter medications are often taken by adults, and given to children, to relieve minor ailments. Despite being freely available from a pharmacy or supermarket, many preparations are of unproven benefit. Some have the potential for harm, especially in the young. Health professionals, as well as parents, have a responsibility to be cautious about giving drugs to children.

Index words: paracetamol, decongestants, pain, fever.

(Aust Prescr 2001;24:149–51)

Introduction

The use of over-the-counter (OTC) medications has become commonplace in Australia. Not only do we, as adults, frequently medicate ourselves with OTC preparations, we give them to our children. The health professions and the community at large often assume that, because these drugs are not regulated by prescription, they are safe, even in overdose. However, the truth may be somewhat more sinister. While some are harmless placebos, others may be causing much more harm than good. Even the ubiquitous paracetamol may slow the body's response to viral infections and, in overdose, it can result in liver failure.

Health professionals need to know about the efficacy and safety of OTC preparations in as much detail as they do about prescription medications. All too often, practitioners will recommend a preparation without sufficient knowledge of its potentially serious adverse effects or the evidence (or lack of) for its use.

Medicines in children

There are fundamental differences between children and adults. Previous generations have treated children as small adults, often with dire consequences.[1] Drug regulatory history is littered with therapeutic misadventure involving children.[2] Nowhere is this plainer than in the story of Reye's syndrome and its association with aspirin, previously thought to be a useful and safe OTC medication for children.

Sugar-free preparations

Much is made of the importance of sugar-free preparations in the marketing of medicines for children. There is a general concern in the community about the effects of sugars upon children's behaviour. However, the only objective harmful effects of sugar are related to the development of dental caries and childhood obesity. Some preparations contain excipients which can be harmful to children with inborn errors of metabolism, e.g. phenylketonuria (PKU).

Decongestants

There is little evidence for the use of either local or systemic decongestants in the symptomatic relief of viral infections. However, they are widely promoted for relieving the symptoms of cold and influenza.

Oral decongestants

A large number of OTC preparations include decongestants. These may be helpful for symptomatic relief of the symptoms associated with viral illnesses. However, prescribers should be aware that many preparations have age restrictions and some are contraindicated in children less than two years old. Often this group of medications is given by parents for their sedative properties. Occasionally, however, children react paradoxically with hyperactivity. Parents should be warned that this effect may last several hours and that further attempts at chemical restraint may only prolong the reaction.

Promethazine

Promethazine is worthy of special mention. Although it is sedating and is used as a remedy for many ailments in children, it can cause paradoxical reactions with hyperactivity in toddlers. Children with epilepsy should use promethazine with caution as it may precipitate seizures. The product information also specifically warns against giving the drug to children under two years old, as its use has been linked to sudden infant death syndrome.[3]

Nasal decongestants

Topical nasal vasoconstrictors have been recommended in the past for babies and children with nasal congestion. In the short term, they will result in the clearing of the nasal passages. Unfortunately, tachyphylaxis may occur after a few days of regular use, and rebound nasal congestion can occur after cessation of the medication. In general, these formulations should be avoided. Intranasal saline solution is a safer alternative (for example 0.5 mL per nostril, one nostril at a time), however, it should be pre-warmed to room temperature (for example in the parent's hands) in case the infant has a particularly sensitive diving reflex leading to bradycardia.

Antitussives

Cough is a common symptom in childhood and is usually related to viral bronchitis and upper respiratory infections.

These conditions are self-limiting and the cough probably serves a useful function in clearing mucus and preventing secondary infection. If a cough is particularly troublesome, other diagnoses should be considered before using an antitussive. Most cough medicines contain a mucolytic, antitussive, decongestant or some combination of these. The only proven antitussives are those containing opioids such as dextromethorphan and codeine. These work by suppressing the cough reflex centrally. Paediatricians do not recommend the routine use of these drugs. Overdose can cause drowsiness.

Analgesics and antipyretics

Paracetamol

Paracetamol is often overused in the treatment of childhood fever[4] and there is a danger of liver toxicity.[5] In spite of these concerns, it should still be considered as first-line treatment for analgesia in children.

Aspirin

Aspirin is contraindicated in children less than 12 years old. Although it is a well-documented analgesic, anti-inflammatory and antipyretic, it has a strong association with Reye's syndrome. Now that the use of aspirin in children has all but ceased, Reye's syndrome has disappeared.[6]

Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug which has recently been marketed as an OTC preparation for children. Its efficacy is probably similar to that of paracetamol and it is currently used as an alternative to paracetamol for the management of pain and fever. While the drugs have similar safety profiles, ibuprofen is associated with a slightly increased risk of gastrointestinal bleeding, even at the low doses used in OTC formulations.[7] There have also been reports of renal toxicity and aspirin-like sensitivity reactions. There is limited experience with this drug in Australia.

Teething gels

An assortment of gels are commonly recommended for relieving the pain and discomfort of teething. While there are complications associated with teething, including drooling, teething gels have failed to demonstrate any specific benefit. It may be that the observed therapeutic effect is related to the actual gum massage. The gels commonly contain salicylic acid, lignocaine, tannic acid, menthol, thymol, glycerol and up to 40% ethanol. Some of these substances have the potential to be harmful in overdose, however teething gels are safe if used as recommended.

Topical applications

Topical moisturising creams and ointments are among the commonest preparations used by parents on their children. However, they are often not considered 'medications' and may not be reported to their physician. Fortunately, most of these products are emollients which can be safely applied to the face and body, and systemic absorption is minimal. They are particularly useful for dry skin and for atopic eczema. In general, ointments are best for dry skin while creams are used for moist lesions.

For atopic eczema, aqueous creams should be applied at least three times a day to all the affected skin. The creams can be used with steroid-containing ointments. They can be used as alternatives to soap for washing, and should also be applied within three minutes of finishing a bath, to the whole body, and face. For very dry lesions, ointments may be more appropriate for trapping moisture in the skin. This can be achieved by adding 10% olive oil or 10% liquid paraffin to the aqueous cream.

In severe eczema, especially if it wakes the child or if there is persistent redness or itching, wet dressings may be appropriate. An alternative is the application of a mixture of 50% liquid paraffin and 50% white soft paraffin (made up by the pharmacist). Adverse effects are uncommon, but some children experience stinging, and blocked pores or pimples and may require temporary discontinuation of the treatment.

Topical steroids

Most of the useful topical steroids are prescription medicines. However, low-potency preparations containing 0.5% hydrocortisone are available OTC. These preparations can be a useful adjunct to moisturisers in cases of mild eczema. Before recommending hydrocortisone a specific diagnosis should be made, and conditions exacerbated by steroids, such as fungal infections, should be excluded. Parents should be advised to seek early review if the treated skin condition fails to respond or worsens.

Antifungal drugs

Infants and children are prone to a range of fungal infestations. Oral infection or secondary infection of nappy rash by *Candida albicans* is common. Topical antifungal drugs such as nystatin or miconazole cream are effective, but need to be continued for a few days after clinical resolution.

Ringworm can occur anywhere on the body and is caused by a range of dermatophytes. The diagnosis can be confirmed by microscopy and culture of skin scrapings. Most cases in children can be treated with topical antifungals such as miconazole. Terbinafine cream is very effective in adults, but is not currently recommended for use in children. Resistant cases, or those involving the scalp or nails, may require systemic therapy.

Rehydrating fluids

One of the great advances in the treatment of gastroenteritis has been the recognition that appropriate oral rehydration is the best form of therapy. Balanced electrolyte solutions can easily be prepared by parents, but the instructions should be carefully followed as over-concentrated solutions can cause osmotic diarrhoea. Compliance may be enhanced by the use of one of the flavoured solutions and by pre-chilling the drink.

Anticolic preparations

Persistent crying, or 'colic' is common in the first three months. Any suspicions of underlying organic disease,

especially of the gastrointestinal (failure to thrive) or urinary tract (fever), should be investigated and excluded before making the diagnosis of colic. Colic has not been proved to be due to 'wind' or 'gas' and may well be a normal developmental phase for many infants. The currently available products contain either simethicone (an anti-gas agent) or a combination of anticholinergics, but none of these has been shown to be effective. In the majority of cases, clinical exclusion of serious pathology and parental reassurance and support is all that is required. However, in severe cases, parental distress exceeds the infant's distress and an effective treatment regimen may include either in-patient or outpatient attendance at a mother/baby unit.

Treatments for reflux

Many infants vomit or posset. This is usually associated with a poorly or incompletely developed lower oesophageal sphincter. In most cases, this is mild and resolves spontaneously with age. In mild cases, posturing and thickened feeds with one of the many available anti-reflux infant feeding formulae may provide symptomatic relief. Severe or persistent cases should be investigated particularly if there is weight loss or failure to thrive.

Complementary and alternative medicines

Complementary medicines such as echinacea and aloe vera are not OTC medicines and are not registered as such. Specific product information is not generally available. Currently in Australia, there is a listing system for these products. This ensures that the manufacturing process complies with certain standards, but no review of efficacy or safety in children is included. Medical practitioners and pharmacists should be aware of the widespread use of complementary medicines.

Sources of information

There are few reliable sources of information on OTC preparations. Practitioners should initially consult the product information[8] and dosing information for many of the medications is available.[8,9,10,11] A few indications covered by the reviews of the Cochrane Collaboration are nasal decongestants for the common cold[12], topical antifungals[13] for skin infections and vitamin C for the common cold.[14] In cases of overdose, the local poisons information centre should be consulted.

Conclusion

OTC medications are commonly used for the temporary relief of minor ailments in children. Some, such as topical moisturisers and oral rehydration fluids, have a real place in therapy. Many, such as the nasal decongestants, are of little use and may have unwanted adverse effects. Others, such as aspirin, are contraindicated in children. Practitioners should question parents about all the therapies that they are giving their children. They should also consult appropriate references before recommending OTC medicines for children.

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Self-test questions

The following statements are either true or false (answers on page 158)

7. Stopping a topical nasal decongestant after prolonged use can cause a reactive hyperaemia in the nose.
8. Promethazine has been associated with sudden infant death syndrome.

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Management of chronic obstructive pulmonary disease (COPD)

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SYNOPSIS

The expiratory airflow obstruction that characterises chronic obstructive pulmonary disease is usually progressive over time and caused by emphysema, obliterative bronchiolitis, and mucus hypersecretion. Stopping smoking is the only measure that slows the progression of chronic obstructive pulmonary disease, and smokers should be encouraged to stop at all stages of the disease. The effects of medication are limited, and need to be balanced against cost and adverse effects. Bronchodilators, given by puffer and spacer rather than by nebuliser, are effective. Avoid inhaled corticosteroids unless there is associated asthma. Pulmonary rehabilitation leads to important improvements in quality of life. Influenza vaccination is helpful. Comorbidity from cardiac disease and sleep disordered breathing are common and can be effectively treated. New therapies under evaluation include lung volume reduction surgery, non-invasive ventilation, and anti-inflammatory drugs.

Key words: smoking, beta agonists, corticosteroids, oxygen.

(Aust Prescr 2001;24:152–5)

Introduction

In chronic obstructive pulmonary disease (COPD), airflow is obstructed during expiration. This increases the work of breathing and causes dyspnoea. In contrast to asthma, the airflow obstruction is not reversible and usually progresses over time. There are several mechanisms of airflow obstruction in COPD. Chronic bronchitis results in hypersecretion of mucus which fills and obstructs the airway lumen. Inflammation and fibrosis of the airway mucosa and surrounding tissue (obliterative bronchiolitis) cause airway wall thickening. Emphysema causes loss of the alveolar attachments which normally hold the airway open.

The aims of management in COPD are therefore to:

- reduce airflow obstruction
- reduce symptoms and improve quality of life
- prevent or reduce secondary medical complications.

The management of COPD involves ongoing assessment and treatment of each of these problems over a long period of time. A consultation checklist is given in Table 1 – try 'SMOKES' in the fight against COPD.

Smoking cessation

Smoking cessation is the only measure known that slows the progression of COPD so it should be considered at all stages of the disease. Medical advice, behavioural management, nicotine replacement therapy and bupropion are important components of effective smoking cessation programs. Even intermittent quitting is better than continued smoking.[1] Successful approaches assess the readiness to quit of the patient, provide individualised education and behavioural strategies, and use nicotine replacement to manage nicotine withdrawal symptoms.

Health professionals have a social responsibility to reduce smoking. They are eyewitnesses to the suffering caused by smoking and need to communicate this to the community, rather than become cynical at the practices of the tobacco industry.

The role of medication

The disease causes chronic disability and the efficacy of drug therapy is limited. Consequently, there is the potential for polypharmacy with its attendant difficulties with compliance, drug interactions and adverse effects. Frequently, resources are allocated to drugs with limited efficacy, while patients are denied interventions such as pulmonary rehabilitation that make a real difference to their quality of life.

Table 1

SMOKES, a consultation checklist for chronic obstructive pulmonary disease

S:	smoking cessation
M:	medication – inhaled bronchodilator, vaccines (influenza, pneumococcus), stop unnecessary treatment (nebuliser, inhaled corticosteroids)
O:	oxygen – is it needed?
K:	komorbidity – cardiac dysfunction, sleep apnoea, osteoporosis, depression, asthma
E:	exercise and rehabilitation
S:	surgery – lung volume reduction surgery, single-lung transplantation

Table 2

Efficacy of interventions for stable chronic obstructive pulmonary disease

	Reduce airflow obstruction	*Reduce symptoms*	*Reduce secondary medical complications*
Smoking cessation	+	+	+
Medications			
Short-acting beta agonist	+	+	–
Anticholinergic	+	+	–
Long-acting beta agonist			
COPD with asthma	+	+	–
COPD without asthma	(+)	(+)	–
Antibiotics	–	–	–
Inhaled corticosteroids	–	–	–
Mucolytics	–	–	–
Oxygen	–	–	+
Rehabilitation	+	+	–

Results of systematic reviews or large randomised clinical trials, accessible by searching the Cochrane Library for 'COPD' and examining the Cochrane Database of Systematic Reviews and Controlled Clinical Trials Register

\+ clinical benefit demonstrated

– clinical benefit not demonstrated. This could be due to ineffective treatment or incomplete evaluation.

(+) statistically significant, but clinical significance unclear

Table 2 shows the effects of medication in stable COPD, based on the results of systematic reviews or large randomised-controlled trials. These results need to be contrasted with a recent audit which showed that 69% of patients were using regular inhaled corticosteroid (a treatment unlikely to be beneficial in COPD), whereas only 27% had completed pulmonary rehabilitation and only 40% had received influenza vaccination.[2] We should stop using ineffective treatment and start using effective management techniques.

Bronchodilators

In an airway that is already narrowed by COPD, normal bronchomotor tone may have an exaggerated constrictor effect on airway narrowing. Bronchodilators relax airway smooth muscle and partially improve airflow obstruction. Short-acting beta agonists improve dyspnoea and airflow obstruction without clear benefit on exercise performance.[3] These drugs can be used alone or in combination with anticholinergics, where an additional benefit may be achieved.

Anticholinergic drugs such as ipratropium bromide improve dyspnoea, airflow obstruction and quality of life in COPD. They have not been shown to improve long-term outcome.

Patients with COPD also benefit from long-acting beta agonists if they have significant bronchodilator reversibility, i.e. asthma. (Most clinicians accept that a bronchodilator response of >15% baseline FEV_1 or >200 mL FEV_1 or >10% predicted FEV_1 indicates asthma.) The role of these drugs in COPD without asthma is less clear[4], and their adverse effects remain a concern. Cardiac arrhythmias can be problematic in severe COPD and long-acting beta agonists may cause a prolonged reduction in serum potassium and potentiate ventricular and atrial premature beats.[5] Careful consideration of the costs and benefits of long-acting beta agonists in patients without asthma is needed before using these drugs in COPD.

Theophyllines are also effective bronchodilators, however adverse effects are frequent. For every seven patients treated, one develops nausea and vomiting (NNV, number needed to vomit, 7).

Drug delivery

Stop using nebulisers!

Drug delivery, by pressurised metered dose inhaler and spacer, has equal efficacy to nebulised treatment. It is cheaper and avoids some of the uncommon adverse effects reported with nebulised therapy: paradoxical bronchoconstriction, glaucoma and systemic effects such as dry mouth and urinary retention.

Antibiotics

The impaired airway defences in COPD allow colonisation by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Typically, these organisms cannot be eradicated from the diseased airway, and so antibiotics are of little use in stable COPD. Some patients with recurrent infective bronchitis (more than three times a year) and persistent purulent sputum may benefit from three months treatment with tetracycline.

COPD is exacerbated by several different causes. Antibiotics are of little benefit if the exacerbation does not have the features of infection. When there is evidence of infection with increased sputum volume, or purulence, fever or a new infiltrate on chest X-ray, then antibiotics can shorten the duration of illness.[6] Streptococcus is sensitive to penicillin. Haemophilus responds to amoxycillin, although between 15% and 30% are penicillin resistant. Macrolides have limited clinical

efficacy in exacerbations due to haemophilus. Moraxella is resistant to penicillins. Amoxycillin with clavulanic acid or doxycycline are effective against each organism.

Annual vaccination against influenza is recommended. Pneumococcal vaccine should be given every five years.

Corticosteroids

Oral corticosteroids are beneficial during exacerbations of COPD, leading to a reduced time in hospital. They have a very limited role in stable COPD. The typical neutrophilic bronchitis that is seen in COPD is not reversed by corticosteroid treatment. *In vitro* evidence raises the possibility that steroids may exaggerate this response by inhibiting neutrophil apoptosis.

About one in five patients responds to a short course of prednisolone. Typically, these patients have an eosinophilic bronchitis[7] as seen in asthma, and this accounts for their favourable response. In order to find who will benefit, patients require a formal trial of prednisolone 30–40 mg daily for 14 days with objective assessment of their response by spirometry. Responders can be considered to have the same pattern of airway inflammation as in asthma, and are treated with ongoing inhaled and oral corticosteroids as required. Steroids should be stopped in non-responders.

Inhaled corticosteroids

Many patients with COPD are prescribed inhaled corticosteroids. The benefits are questionable[8], whereas the potential for adverse effects is real. A review of 10 trials of short-term inhaled corticosteroids in COPD found no significant improvement in lung functions.[9] In mild COPD, two large trials have shown that inhaled corticosteroids do not prevent long-term progression of the disease. There may be an initial improvement in lung function, but this is not sustained. One study conducted in patients with more severe COPD showed a reduction in moderate to severe exacerbations, however methodological problems have limited the interpretation of these data. Regular inhaled corticosteroids in stable COPD without an asthmatic component are of questionable efficacy and have the potential for adverse effects. The cost is also considerable.

Mucolytics

Treating mucus hypersecretion shortens the duration of disability during exacerbations by about 0.65 days per month. The clinical significance and cost-effectiveness of mucolytics are unclear.[2] Physiotherapy is effective in removing excessive airway secretions but has no clear effect on lung function.

Oxygen

Long-term domiciliary oxygen therapy can reduce mortality in hypoxaemic COPD. Consequently it is important to identify and treat patients with hypoxia (by blood gases or pulse oximetry) as well as the effects of hypoxia (polycythaemia, cor pulmonale).[10]

Rehabilitation

Behavioural management of chronic dyspnoea and the resultant physical deconditioning are important aspects of management. Pulmonary rehabilitation programs address these issues and lead to increased exercise tolerance, increased exercise ability, reduced dyspnoea and improved quality of life.[11] The key parts of pulmonary rehabilitation are:

- exercise training
- education
- psychosocial/behavioural intervention
- outcome assessment.

Each part should be systematically addressed in all patients with moderate or severe COPD. This can be achieved by referral to an established program, or by a series of consultations between the patient, doctor and allied health staff. Although low body weight is associated with impaired pulmonary function, clinical trials have not shown that nutritional supplements are beneficial.

Comorbidity

COPD is a long-term problem, and patients may acquire several other conditions during their life. These may be exacerbated by COPD, affected by drugs for COPD, or cause symptoms that increase disability in COPD. A high index of suspicion needs to be maintained for comorbid conditions in COPD.

Left ventricular dysfunction is common and can cause an exacerbation of dyspnoea. Primary cardiac disease (coronary artery disease, hypertension) may coexist with COPD and a dilated right ventricle can impair left ventricular diastolic function.

Sleep disordered breathing can be a problem in COPD, particularly during REM sleep. Sleep studies are indicated when there is a suspicion of sleep apnoea, or when cor pulmonale and/or polycythaemia are present but not explained by daytime oxygen levels.

Anxiety and depression occur in up to 30% of patients with COPD, leading to impaired functional capacity and quality of life. In one study of severe COPD, walking distance and functional ability were better related to the presence of depression than the degree of airflow obstruction.

Osteoporosis complicates COPD and corticosteroid therapy. A crush fracture or rib fracture constitute major events for a person with COPD. Prevention of osteoporosis is important and starts with avoiding unnecessary treatment, particularly corticosteroids.

Novel approaches

Lung volume reduction surgery involves resection of emphysematous parts of the lungs, typically in the upper lobes. This reduces hyperinflation and improves the mechanical efficiency of the respiratory muscles. Potentially suitable patients are those who have completed a pulmonary rehabilitation program, have predominantly upper lobe emphysema with little comorbidity, who accept that the

long-term outcomes and comparative efficacy are unknown, and who understand and accept the local perioperative mortality rate (5–15% is considered acceptable).[12]

Non-invasive ventilation is a major advance for the management of hypercapnic/acidotic exacerbations of COPD. The benefits in stable COPD with respiratory failure are being evaluated in an Australian multicentre trial. Several experimental drugs are being evaluated for their effects on airway inflammation and extracellular matrix destruction in COPD.

Conclusion

COPD is a chronic and disabling condition caused by smoking. Disability can be minimised by a systematic approach to management that emphasises the use of safe, effective medications, withdraws unsafe or ineffective therapy, and attends to the effects of physical deconditioning and psychosocial distress through rehabilitation.

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FURTHER READING

See resources on the following web sites:
http://www.aacvpr.org
http://www.goldcopd.com

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 158)

9. Inhaled corticosteroids produce a sustained improvement in lung function in most patients with chronic obstructive pulmonary disease.
10. Giving a beta agonist by nebuliser is more effective than giving it by metered dose inhaler and spacer.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

Cetrorelix acetate

Cetrotide (Serono)

vials containing 250 microgram or 3 mg as powder for reconstitution

Approved indication: assisted reproduction

Australian Medicines Handbook Section 10.6.3

Luteinising hormone has an important role in the menstrual cycle. In assisted reproduction programs a premature surge in luteinising hormone can cause ovulation, and therefore disrupt the collection of oocytes. This surge can be prevented by antagonising luteinising hormone releasing hormone (LHRH).

Cetrorelix competes with LHRH for binding sites in the pituitary gland. This reduces the secretion of luteinising hormone and follicle stimulating hormone. A 250 microgram dose is injected every day starting five or six days after ovarian stimulation is begun. These injections continue until the day before ovulation is induced. A single large dose (300 mg) can be used to suppress ovulation for at least four days.

Analogues of gonadotrophin-releasing hormones have also been used to prevent surges of luteinising hormone. (Prolonged administration of an analogue agonist eventually reduces gonadotrophin production.) Cetrorelix has therefore been compared with the LHRH agonists such as triptorelin and buserelin. While cetrorelix was as efficacious as the agonists it has the advantage of a more immediate action.

The most frequent adverse effects of cetrorelix are injection site reactions. Ovarian hyperstimulation can occur, but it is uncertain if this is caused by cetrorelix rather than the hormones used to promote follicular development. Compared to patients given LHRH agonists there are fewer cases of ovarian hyperstimulation.

While cetrorelix has been approved for use by specialists in the management of female infertility, researchers are studying other possible uses of LHRH antagonists.

Ganirelix

Orgalutran (Organon)

250 microgram/0.5 mL in pre-filled syringes

Approved indication: assisted reproduction

Australian Medicines Handbook Section 10.6.3

Ganirelix is the second member of its class to be approved for use in Australia. The first luteinising hormone releasing hormone (LHRH) antagonist to be approved was cetrorelix (see above).

These drugs are given to prevent premature ovulation when controlled ovarian hyperstimulation is used to assist conception. The patients are given follicle stimulating hormone (FSH) starting on the second or third day of their menstrual cycle. When they have their sixth dose of FSH they start daily subcutaneous injections of ganirelix. By binding to pituitary gonadotrophin receptors, ganirelix inhibits a surge in the concentration of luteinising hormone. By preventing this surge, the timing of ovulation can be controlled. This enables an adequate number of follicles to develop to the required size for collection.

Earlier attempts to create gonadotrophin antagonists had problems because they triggered allergic reactions by releasing histamine. Although this does not appear to occur with ganirelix, it can cause reactions at the injection site in up to 15% of patients. Other adverse effects include headache and nausea.

The efficacy of ganirelix is probably similar to that of the gonadotrophin agonists which have also been used to prevent surges of luteinising hormone. Ganirelix has the advantage of acting more quickly. There is, however, a concern that implantation rates may be reduced for follicles exposed to LHRH antagonists.[1]

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Lercanidipine hydrochloride

Zanidip (Solvay)

10 mg film-coated tablets

Approved indication: hypertension

Australian Medicines Handbook Section 6.4.6

Lercanidipine is a dihydropyridine calcium channel antagonist. Four other dihydropyridines are already available in Australia (see 'Calcium channel antagonists' Aust Prescr 1997;20:5-8).

Like other dihydropyridines, lercanidipine relaxes vascular smooth muscle to lower peripheral resistance. This vasodilatation occurs slowly so patients are less likely to develop acute hypotension and reflex tachycardia.

Although lercanidipine is completely absorbed its bioavailability is reduced to 10% by first-pass metabolism. The tablets should be taken at least 30 minutes before a meal because food increases the bioavailability. As the enzymes involved in the first-pass metabolism can become saturated, doubling the dose causes the plasma concentrations to more than double.

Lercanidipine is eliminated by liver metabolism. It is completely metabolised with approximately half the metabolites being excreted in the urine. This metabolism involves cytochrome P450 3A4 so the plasma concentration of lercanidipine may be increased by drugs, such as erythromycin, fluoxetine and ketoconazole, which inhibit the enzyme. The plasma concentration may be reduced by drugs, such as phenytoin and carbamazepine, which induce CYP 3A4. Lercanidipine is contraindicated in patients with moderate or severe liver disease and in patients with severe renal impairment. Although the half-life of lercanidipine is relatively short, its antihypertensive effect is sustained for 24 hours.

Short-term studies show that lercanidipine reduces diastolic blood pressure by 5-7 mmHg more than a placebo. During comparative studies lasting 12-16 weeks no significant differences emerged between lercanidipine and slow-release nifedipine, atenolol, hydrochlorothiazide or captopril. In a double-blind crossover study of 16 patients, lercanidipine reduced diastolic blood pressure by 13 mmHg while amlodipine produced a 10 mmHg reduction.[1]

Many of the adverse effects of lercanidipine are caused by vasodilatation. Headache, flushing and palpitations are the commonest adverse reactions. As most studies have only lasted a few months, more information is needed on the long-term safety of lercanidipine. Given the concerns about the adverse effects of dihydropyridines[2], it is unlikely that lercanidipine will have a prominent role in the treatment of hypertension.

Although it appears to be effective for mild to moderate hypertension it is not indicated for severe hypertension.

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Lopinavir/ritonavir

Kaletra (Abbott Australia)

capsules containing 133.3 mg lopinavir/33.3 mg ritonavir

oral solution containing 400 mg lopinavir/100 mg ritonavir in 5 mL

Approved indication: HIV

Australian Medicines Handbook Section 5.3

Combinations of antiviral drugs which include a protease inhibitor effectively suppress HIV. By inhibiting viral proteases drugs, such as ritonavir, reduce replication of the virus.

Lopinavir is also a protease inhibitor. After absorption it undergoes high first-pass metabolism and is rapidly cleared from the circulation. Lopinavir is extensively metabolised by cytochrome P450 3A. This is one of the enzymes inhibited by ritonavir, so giving ritonavir in combination with lopinavir increases the plasma concentrations of lopinavir.

The combination should not be prescribed with drugs such as triazolam, midazolam, simvastatin, lovastatin, ergot derivatives, cisapride or rifampicin. Other drugs with potentially significant interactions include atorvastatin, cerivastatin, dihydropyridines, oral contraceptives, sildenafil and warfarin. Patients should not take St John's wort as this reduces the plasma concentrations of lopinavir/ritonavir.

A randomised double-blind trial has studied lopinavir/ritonavir in combination with stavudine and lamivudine in patients who have not been previously treated with antiretroviral drugs. After 48 weeks of treatment the concentration of HIV RNA had fallen below 400 copies/mL in most patients.[1]

In a comparison with nelfinavir, another protease inhibitor, lopinavir/ritonavir was given to patients who also took stavudine and lamivudine. After 24 weeks the HIV RNA was below 400 copies/mL in 71% of the patients taking nelfinavir and in 79% of those taking lopinavir/ritonavir. This difference is statistically significant.

Lopinavir/ritonavir has also been studied in patients previously treated with a protease inhibitor. It has been given in a regimen with two nucleoside reverse transcriptase inhibitors and nevirapine (a non-nucleoside reverse transcriptase inhibitor). After 72 weeks, 75% of the patients had less than 400 copies/mL.

Approximately 3% of the patients withdrew from clinical trials of lopinavir/ritonavir because of adverse reactions. Diarrhoea affects 14-22% of patients. Other adverse effects include nausea, abdominal pain and asthenia. The combination alters liver function and can also increase concentrations of total cholesterol and triglycerides. Possibly related to the changes in triglycerides, are reports of pancreatitis in patients taking lopinavir/ritonavir.

Although lopinavir/ritonavir can be used to treat patients who have previously been treated with a protease inhibitor the extent of cross-resistance is uncertain. Some viruses will develop a reduced sensitivity to lopinavir/ritonavir during treatment.

Lopinavir/ritonavir may have a role in treating patients who are infected with HIV that is resistant to other drugs. Its precise role and the most suitable regimen will need further study as there are no data about the clinical outcomes of treatment.

REFERENCE

1. Murphy RL, Brun S, Hicks C, Eron JJ, Gulick R, King M, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naive adults with HIV-1 infection: 48-week results. AIDS 2001;15:F1-F9.

Meningococcal group C conjugate vaccine

Meningitec (Wyeth)

vials containing 0.5 mL

Approved indication: immunisation

Australian Medicines Handbook Section 20.1

Neisseria meningitidis is a major cause of meningitis and infants are particularly at risk. Babies are not currently immunised against the meningococcus because the available polysaccharide vaccines are not very effective. Conjugating the meningococcal group C oligosaccharide to diphtheria protein increases the immune response.[1] Immunogenicity data enabled this conjugate vaccine to be approved in the UK, without a trial of the vaccine's efficacy.

A randomised controlled trial compared a conjugate vaccine with a quadrivalent polysaccharide vaccine in 127 infants aged 15-23 months. Each child had two injections two months apart, followed by a booster dose of polysaccharide vaccine a year later. After two doses the IgG response in the children who received conjugate vaccine was 10 times greater than the response to the polysaccharide vaccine. Their titres were still twice as high one year later. One month after the booster their titres were 50 times greater than those of the children who had the polysaccharide vaccine.[2]

Meningococcal group C conjugate vaccine is now part of the routine immunisation schedule in the UK. A study of the first nine months of experience with the vaccine estimated the short-term efficacy of a single dose to be 92% for toddlers and 97% for adolescents. Only two of the 32 toddlers who developed meningitis had been immunised.[3] There are no efficacy data for infants who receive a course of three injections.[3]

The injections are given intramuscularly. Meningococcal vaccine can be given at the same time as routine childhood vaccines, but there is limited information about giving it with inactivated polio vaccine or varicella vaccine.

Injection site reactions are common. Some children will develop a fever in excess of 38°C and there may be signs of irritability. Convulsions have been reported.

While the conjugate vaccine appears to be safe and effective in the short term, it will not protect people against other causes of meningitis, for example *Neisseria meningitidis* group B which is more common in Australia.

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2. MacDonald NE, Halperin SA, Law BJ, Forrest B, Danzig LE, Granoff DM. Induction of immunologic memory by conjugated vs plain meningococcal C polysaccharide vaccine in toddlers. JAMA 1998;280:1685-9.
3. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001;357:195-6.

Moxifloxacin hydrochloride

Avelox (Bayer)

400 mg tablets

Approved indication: respiratory infections

Australian Medicines Handbook Section 5.1.12

Moxifloxacin is a fluoroquinolone antibiotic. Like other fluoroquinolones it is active against Gram-negative bacteria such as *Haemophilus influenzae*. Compared to older members of the class, such as ciprofloxacin, moxifloxacin has more activity against Gram-positive bacteria such as *Streptococcus pneumoniae*.

Given its spectrum of antibacterial activity moxifloxacin has been approved for the treatment of community-acquired pneumonia, exacerbations of chronic bronchitis and sinusitis. In studies of patients with community-acquired pneumonia, moxifloxacin has been as effective as other drugs such as clarithromycin.

Moxifloxacin is as effective as cefuroxime in the treatment of acute maxillary sinusitis. Cefuroxime was also equivalent to moxifloxacin in the treatment of exacerbations of chronic bronchitis. For this indication, a five day course of moxifloxacin is as effective as a seven day course of clarithromycin.

Moxifloxacin has a half-life of 12 hours, but can be given once a day. It is eliminated by renal and hepatic clearance. The metabolism of moxifloxacin does not involve the cytochrome P450 system. Although it has not been associated with the severe liver problems associated with trovafloxacin, moxifloxacin should not be given to patients with significant hepatic impairment.

Like other oral antibiotics, nausea, vomiting and diarrhoea are common adverse effects of moxifloxacin. It may cause dizziness and lightheadedness so patients should know how they react to this drug before they drive or operate machinery. Moxifloxacin can also prolong the QT interval so there is a potential for arrhythmias. Similar ECG changes led to the withdrawal of grepafloxacin. Moxifloxacin should therefore not be given to patients with a prolonged QT_c interval, hypokalaemia, or those taking drugs which prolong the QT_c interval. Although the photosensitivity potential of moxifloxacin appears to be low, hypersensitivity reactions can occur after the first dose.

Bacteria are becoming resistant to the fluoroquinolones and there is cross-resistance to drugs within the class. To maintain the usefulness of these drugs, moxifloxacin should probably not be used as a first-line treatment for common infections such as sinusitis.

Thyrotropin alfa-rch

Thyrogen (Genzyme)

0.9 mg/mL in 5 mL vials

Approved indication: thyroid cancer testing

Australian Medicines Handbook Section 10.3

This recombinant form of human thyroid stimulating hormone (TSH) can be used in diagnostic tests of patients with thyroid cancers. One indication, in conjunction with radioactive iodine imaging, is for the detection of remnant thyroid tissue after total thyroidectomy. The radioiodine is given 24 hours after the second of two intramuscular injections of reconstituted thyrotropin (also given 24 hours apart). A similar regimen is used for thyroglobulin testing with a serum sample being taken 72 hours after the second injection. (Thyroglobulin should be undetectable after total thyroidectomy.)

The common adverse effects of thyrotropin are nausea and headache.

NEW FORMULATIONS

Calcipotriol

Diavonex Scalp Solution (CSL)

50 microgram/mL solution

Gliclazide

Diamicron MR (Servier)

30 mg modified-release tablets

NEW STRENGTH

Conjugated oestrogens/ medroxyprogesterone acetate

Premia 10 (Wyeth)

packs of 14 tablets containing 0.625 mg conjugated oestrogens and 14 tablets containing 0.625 mg conjugated oestrogens/ 10 mg medroxyprogesterone acetate

NEW COMBINATION

Abacavir/lamivudine/zidovudine

Trizvir (GlaxoSmithKline)

tablets containing 300 mg abacavir/150 mg lamivudine/ 300 mg zidovudine

NEW PROPRIETARY BRANDS

Cefotaxime sodium

DBL Cefotaxime Sodium for Injection (Faulding)

500 mg, 1 g and 2 g vials

Gliclazide

Nidem (Arrow)

80 mg tablets

Answers to self-test questions

1. False	3. True	5. True
2. True	4. False	6. True
7. True	9. False	
8. True	10. False	

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