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CONTENTS

Editorial

Pharmaceutical free trade: will it be fair?

John S. Dowden, Editor, Australian Prescriber

Key words: drug industry, drug regulation, Pharmaceutical Benefits Scheme.

(Aust Prescr 2004;27:54–5)

Australia and the USA concluded a free trade agreement in February 2004.[1] The USA has negotiated duty-free access for all its farm exports and 99% of its manufactured goods.

An issue of concern in the negotiations was the Australian Pharmaceutical Benefits Scheme (PBS). As the PBS covers the whole community, the Australian Government has a strong bargaining position when it comes to negotiating drug prices. Combined with policies such as reference pricing, this has resulted in Australia having low drug prices relative to most other developed nations.

It has been argued that the current Australian system reduces the profitability of the pharmaceutical industry. As many drug companies are based in the USA they could be expected to hope that the free trade agreement would improve their fortunes in Australia. Whether or not the local pharmaceutical industry will benefit to the same degree as the US companies is unclear.

The pharmaceutical part of the agreement (Annex 2-C) does not appear to contain any drastic changes, but it is open to interpretation. The agreed principles are focused on timely access to innovative pharmaceutical products. This means new drugs must be expeditiously evaluated. There is no suggestion at this stage that the Therapeutic Goods Administration (TGA) will automatically approve drugs which have already been approved by the US Food and Drug Administration. However, there is to be increased regulatory co-operation between the USA and Australia, 'with a view to making innovative medical products more quickly available to their nationals'.

It remains to be seen whether a decision by the TGA not to approve a new drug or a decision not to list the drug on the PBS could be construed to be a breach of the agreement, resulting in referral to the dispute resolution process. In this situation, could it be argued that Australia has not honoured its commitment 'to recognise the value of innovative pharmaceuticals'?

The pharmaceutical industry has been pushing for greater openness in the processes for listing drugs on the PBS. Its efforts have been rewarded with six points of Annex 2-C devoted to transparency. They include the establishment of an independent review process to examine recommendations for listing drugs. The agreement does not specify whether or not this is an appeals mechanism which can overturn decisions. It is also unclear if the review process will be confidential. If the review process is a move towards greater transparency, it will be interesting to know if the drug companies will agree to open assessment of the data supporting their claims. If drugs are going to have a public subsidy, making the data available for public scrutiny is highly desirable.

Part 5 of Annex 2-C allows drug companies to disseminate information to consumers via the internet. Although this activity is regulated by the laws of each country, Australia now has trade agreements with the two westernised countries (New Zealand and USA) that allow direct-to-consumer advertising.[2]

Other parts of the agreement also have an impact on pharmaceuticals. Chapter 17 deals with intellectual property rights and several paragraphs refer specifically to pharmaceutical products.[1] Patents can be extended to account for the time the regulatory authorities take to evaluate a drug. Companies which want to market drugs that are the same or similar to innovator products will not be able to do so for at least five years from the date the innovator product is marketed, unless the innovator company gives permission.

Australia has committed to strict standards regarding intellectual property and patents, but it is not clear whether the bilateral agreement overrides other agreements on intellectual property. In 2001 the World Trade Organization declared that the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) should be interpreted and implemented in a

In this issue…

The free trade agreement between Australia and the USA may have benefits for both countries, but the impact on pharmaceuticals is unclear. Will Australia have earlier access to drugs such as the thiazolidinediones or will there be more work for the advertising watchdogs?

Beneficial treatments do not have to be new and expensive. For example, Geoff McColl tells us glucosamine can help people with arthritis of the knee.

New problems can arise with older drugs. Hester Wilce explains why temazepam gelcaps have been withdrawn from Australia, and Greg Roberts reminds us how to use thyroxine correctly.

manner supportive of the 'right to protect public health and, in particular, to promote access to medicines for all'.[3] The US-Australia agreement does not mention equity of access or the quality use of medicines.

The details of the agreement will probably depend on the Medicines Working Group, which will be established 'to promote discussion and mutual understanding of the issues'. It is unknown if these discussions will be secret, but the only members of the Medicines Working Group will be officials from federal government agencies.

If the official line is that there will be no changes to the PBS, then why were pharmaceuticals included in the agreement? The USA has a legislative requirement for negotiations 'to achieve the elimination of government measures such as price controls and reference pricing which deny full market access for United States products'.[4] Is the US-Australia agreement an exception to this rule? If it is not, inclusion of pharmaceuticals in the agreement could eventually prove to be a costly mistake with potentially adverse consequences for public health.

References

1. Department of Foreign Affairs and Trade Australia – United States Free Trade Agreement. Canberra: Department of Foreign Affairs and Trade; 2004. http://www.dfat.gov.au/trade/negotiations/us_fta/text/ [cited 2004 May 14]
2. Vitry A. Is Australia free from direct-to-consumer advertising? Aust Prescr 2004;27:4-6.
3. World Trade Organization. Declaration on the TRIPS agreement and public health. Geneva: World Trade Organization; 2001.
4. Trade Act of 2002 (USA). Section 2102.

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Are new drugs as good as they claim to be?

Editor, – It was disappointing to read that there are still people questioning the gastrointestinal safety and cost-effectiveness of the COX-2 inhibitors (Aust Prescr 2004; 27:2–3). It is even more disappointing when this opinion is referenced to a single non-systematic, heterogenous review article (that is, evidence level 5), which misrepresents the body of evidence in two important ways.

The review claims that non-steroidal anti-inflammatory drugs (NSAIDs) have minimal benefit against which to compare their adverse events. This is based on a very selective use of analgesic data from the literature (which still showed a significant difference to placebo). An alternative view is that NSAIDs are the mainstay of therapy worldwide for the symptomatic relief of arthritis and occupy the first five top rankings for analgesics on the Oxford pain relief table because of their clinical benefits.[1] This is backed by clinical trials where both COX-2 inhibitors and traditional NSAIDs showed statistically and clinically different efficacy to placebo in arthritis.[2,3,4,5]

The article by Wright also states that there is no evidence for reduced gastrointestinal damage from COX-2 inhibitors. He bases this opinion on a single flawed study (CLASS) that had a statistical power of about 45% (that is, less than a 50% chance of detecting any real differences).[6] He neglects to mention the wealth of other data from adequately powered studies that show a significant difference in safety and tolerability between celecoxib and the non-specific NSAIDs.[7,8,9,10,11,12,13]

If the COX-2 inhibitors did not represent a cost-effective treatment then they would not be listed on the Pharmaceutical Benefits Scheme. The Pharmaceutical Benefits Advisory Committee makes this decision based on evidence, not opinion.

Dr Simon McErlane
Medical Director
Pfizer Global Pharmaceuticals
Pfizer Australia

References

1. Oxford league table of analgesics in acute pain. http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html [cited 2004 May 14]
2. McKenna F, Borenstein D, Wendt H, Wallemark C, Lefkowith JB, Geis GS. Celecoxib versus diclofenac in the management of osteoarthritis of the knee. Scand J Rheumatol 2001;30:11-8.
3. Gibofsky A, Williams GW, McKenna F, Fort JG. Comparing the efficacy of cyclooxygenase 2-specific inhibitors in treating osteoarthritis: appropriate trial design considerations and results of a randomized, placebo-controlled trial. Arthritis Rheum 2003;48:3102-11.
4. Simon LS, Weaver AL, Graham DY, Kivitz AJ, Lipsky PE, Hubbard RC, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. JAMA 1999;282:1921-8.
5. Weisman MH. Double-blind randomized trial of diclofenac sodium versus placebo in patients with rheumatoid arthritis. Clin Ther 1986;8:427-38.

6. Wright JM. The double-edged sword of COX-2 selective NSAIDs. CMAJ 2002;167:1131-7.
7. Singh G, Goldstein J, Bensen W, Agrawal N, Eisen G, Fort J, et al. SUCCESS-1 in osteoarthritis (OA) trial: celecoxib significantly reduces the risk of serious upper GI complications compared to NSAIDs while providing similar efficacy in 13,274 randomized patients [poster presented at EULAR; 2001 June 13-16; Prague].
8. Goldstein JL, Silverstein FE, Agrawal NM, Hubbard RC, Kaiser J, Maurath CJ, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. Am J Gastroenterol 2000;95: 1681-90.
9. Mamdani M, Rochon PA, Juurlink DN, Kopp A, Anderson GM, Naglie G, et al. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. Br Med J 2002;325:624.
10. Chan FK, Hung LC, Suen BY, Wu JC, Lee KC, Leung VK, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. N Engl J Med 2002;347:2104-10.
11. Bensen WG, Zhao SZ, Burke TA, Zabinski RA, Makuch RW, Maurath CJ, et al. Upper gastrointestinal tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo. J Rheumatol 2000;27:1876-83.
12. McKenna F, Arguelles L, Burke T, Lefkowith J, Geis GS. Upper gastrointestinal tolerability of celecoxib compared with diclofenac in the treatment of osteoarthritis and rheumatoid arthritis. Clin Exp Rheumatol 2002;20:35-43.
13. Goldstein JL, Eisen GM, Burke TA, Pena BM, Lefkowith J, Geis GS. Dyspepsia tolerability from the patients' perspective: a comparison of celecoxib with diclofenac. Aliment Pharmacol Ther 2002;16:819-27.

Associate Professor J. Lexchin, the author of the editorial, comments:

Dr McErlane dismisses the results of the CLASS study on celecoxib by claiming that it was underpowered to find significant benefits. CLASS was funded by Pharmacia, the company that marketed celecoxib, and the corresponding author was a Pharmacia employee. Pharmacia is now owned by Pfizer. If there was a problem with the design of CLASS then Dr McErlane should look to his own house.

He criticises the article by Dr Jim Wright for ignoring seven articles showing the gastrointestinal benefits of COX-2 inhibitors. However, one was a poster presentation that was otherwise unpublished and two were published either just before or after Dr Wright's piece and would have been unavailable to him.

Dr McErlane has misread Wright's article. Wright does not say that COX-2 drugs have minimal benefits; what he does say is that the benefits need to be seen in the context of serious adverse events from these drugs. Serious adverse events include not only gastrointestinal problems but other adverse events. Wright combines all serious adverse events as reported in the CLASS study for celecoxib and for other NSAIDs and shows that there is no statistical difference in serious adverse events between celecoxib and the other NSAIDs. In other words, whatever reduction in gastrointestinal harms celecoxib produced was offset by a higher incidence of other serious adverse events.

Dr McErlane's letter provides a good lesson in why doctors should not rely solely on what companies have to say about their products.

Prescribing issues for Aboriginal people

Editor, – I read with interest the paper 'Prescribing issues for Aboriginal people' (Aust Prescr 2003;26:106–9). My research into the practice of remote area nursing shows that there are serious problems in the acquisition and use of drugs in remote Aboriginal settings.

I would like to draw your attention to the initiatives taken in Queensland. Unlike the standard treatment manual referred to in the article, a 'Primary Clinical Care Manual' (3rd ed. 2003) has been developed by the Queensland Nursing Council, Royal Flying Doctor Service and Queensland Health, based on statutory regulations, for use by nurses authorised in isolated practice. Under State legislative provisions of the Health (Drugs and Poisons) Regulation 1996, a process is in place for the formal endorsement of nurses in isolated practice areas and for indigenous health workers with specific protocols clarifying their separate responsibilities in relation to drugs and drug use.

Jennifer Cramer
Registered nurse
Perth

Ibuprofen use

Editor, – Over the past five years the use of ibuprofen to treat fever in children has increased dramatically at the Royal Children's Hospital, Melbourne. This is demonstrated by a seven-fold increase in the purchases of ibuprofen packs/year from 1999 to 2003 (Fig.1). Paracetamol usage and purchase has remained essentially unchanged over the same period, and there has been no significant change in the number or type of patients seen at our hospital. This continually increasing shift in practice has occurred despite the fact that there has been no change in hospital policy on the use of non-steroidal anti-inflammatory drugs. Furthermore, a monthly audit of ibuprofen use on our general paediatric ward showed that 36 of 38 prescriptions for ibuprofen also included paracetamol.

This change in practice may be a combination of three factors. Number one being aggressive marketing of ibuprofen by the drug company, second the change of ibuprofen syrup from Schedule 4 to Schedule 2 in 1998, and finally an increase in the number of British-trained doctors working in our institution. Ibuprofen is far more commonly used in Britain than Australia.

This therapeutic drift is occurring despite a lack of evidence to support it. Paracetamol has been used far more extensively worldwide than ibuprofen, so much so that the risks associated with the use of paracetamol are well known. The same cannot be said for ibuprofen use in children. Ibuprofen has no demonstrated advantages over paracetamol for the treatment of fever, nor has the combined use of these drugs been shown to be of benefit. In fact the combination may lead to an increased incidence of serious adverse effects and confusion regarding their correct dosing.[1,2,3,4]

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Associate Professor Noel Cranswick
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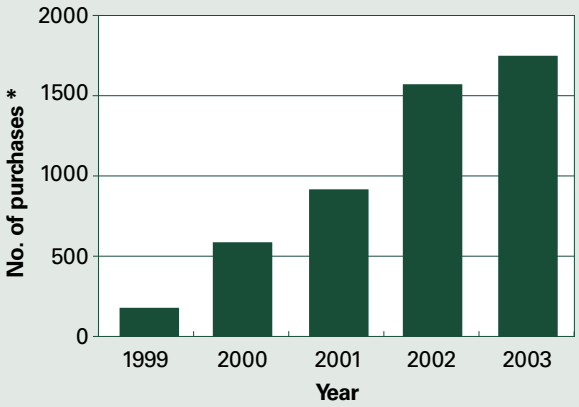
Fig. 1

Ibuprofen purchases



* Individual packs (tablets or syrup)

References

1. Walson PD, Galletta G, Chomilo F, Braden NJ, Sawyer LA, Scheinbaum ML. Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. Arch Pediatr Adolesc Med 1992;146:626-32.
2. McCullough HN. Acetaminophen and ibuprofen in the management of fever and mild to moderate pain in children. Paediatr Child Health 1998;3:246-51.
3. Mayoral CE, Marino RV, Rosenfeld W, Greensher J. Alternating antipyretics: is this an alternative? Pediatrics 2000;105:1009-12.
4. Lesko SM, O'Brien KL, Schwartz B, Vezina R, Mitchell AA. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001;107:1108-15.

Hyponatraemia

Editor, – I think there is an unintentional inaccuracy in the Summary of the article 'Managing drug-induced hyponatraemia in adults' (Aust Prescr 2003;26:114–7).

The first sentence of the Summary states that 'drug-induced hyponatraemia occurs in approximately 5% of outpatients...' but the source for this statement seems to be the Introduction which merely states that: 'A Melbourne laboratory found hyponatraemia in 4.8% of 326 923 samples from ambulatory patients ...'.

Obviously the Melbourne sample is not representative of the whole population of ambulatory patients, or outpatients, as implied by the statement in the Summary. It is only a sample of patients who merited a blood sample being sent to the laboratory. Presumably these patients were sick enough for their general practitioner to investigate (we could call them 'sick outpatients'), and there is no account taken of all the ambulatory patients who did not have samples taken ('well outpatients'). The proportion of 'sick outpatients' who have samples sent to a laboratory is very small, surely less than 10% of the whole and probably much less than that. The problem with the statement in the Summary is that it is likely to be cited (especially when it appears in an authoritative publication like *Australian Prescriber*) but quoted out of context and so could mislead. It is certain, surely, that the proportion of outpatients with hyponatraemia is much less than 5%. Frankly, I'd be surprised if it was more than 0.5%.

Stuart Baker
Pharmacist
Mortlake, Vic.

Dr S. Fourlanos and Dr P. Greenberg, the authors of the article, comment:

We thank Mr Baker for drawing our attention to misinterpretation of the first sentence of the Summary.

We hope that other readers, like him, will have read in the Introduction the selection process for the patients referred to in the Summary.

We agree that the first sentence of the Summary should read: 'Hyponatraemia occurs in approximately 5% of ambulatory and 14% of admitted patients referred for blood tests by general practitioners'.

The prevalence of hyponatraemia in other non-admitted patients and in the broader community is also unknown to us.

Temazepam capsules: what was the problem?

Hester Wilce, General Practitioner, Kings Cross, Sydney

Summary

Over the last few years, injecting drug users in Australia increasingly injected the contents of temazepam gelcaps, an activity associated with significant harm. Although changes to the Pharmaceutical Benefits Scheme in May 2002 reduced the prescription of gelcaps, they did not eliminate misuse. Temazepam capsules were withdrawn from the Australian market in March 2004. Already front-line services are reporting a decrease in harm and misuse.

Key words: adverse effects, drug dependence, benzodiazepines, hypnotics.

(Aust Prescr 2004;27:58–9)

Introduction

Until recently, temazepam was available in Australia as a tablet and as a soft gelatin capsule (gelcaps). There is little evidence that there was any clinical reason to prescribe gelcaps instead of tablets.[1] There was evidence of an increase in intentional misuse, abuse, dependency and complications related to the injection of the liquid contents of temazepam gelcaps.

Research evidence

The intravenous misuse of temazepam was first reported in Scotland in 1987.[2] International research has shown that temazepam, flunitrazepam and diazepam are the preferred benzodiazepines among injecting drug users. The practice of injecting benzodiazepines, and in particular the contents of temazepam gelcaps, is potentially very harmful and is a significant health issue for injecting drug users.[3,4]

Studies undertaken in Sydney found that benzodiazepines were commonly injected by people who also injected amphetamines or heroin, with diazepam and temazepam being the most likely to be injected.[5] Another study in Southwest Sydney found 25% of injecting drug users had injected benzodiazepines at some time and that temazepam was the most commonly injected.[6] A study in 2002 in Sydney found that while levels of methadone injection had fallen, there had been no decline in the proportion of injecting drug users injecting benzodiazepines.[7] In the Kings Cross area of Sydney, there were anecdotal reports of an increasing problem with the injection of temazepam gelcaps and its associated harms since the heroin shortage in early 2001.[8]

Physical complications associated with the injection of temazepam gelcaps (Table 1)

Temazepam is insoluble in water and there is evidence that it directly damages vascular epithelium. This means that both the gelcap and tablet formulations are harmful when injected. Gelcaps were preferentially injected because injecting drug users felt that they worked better than tablets and the contents were in a readily injectable form. They heated the capsules and then drew the contents up into a syringe.

A survey of users of multiple drugs in the Kings Cross area who injected temazepam gelcaps found that the majority injected up to 200 mg daily. The gelcaps were obtained from doctors and on the street. The users injected gelcaps to replace or enhance the effects of heroin, to offset effects of psychostimulants such as cocaine or methamphetamine, to deal with stress or psychological distress and/or to sleep. They injected because the effect was quicker and more intoxicating.

All those surveyed were aware of the risks of injecting. Most had suffered some complications in the past including abscesses, cellulitis, skin ulcers, nerve damage and distal limb amputation. A number reported using deep veins in the groin and neck because they could no longer access peripheral veins.

Physical complications associated with the injection of temazepam gelcaps

- thrombophlebitis
- compromised venous return leading to lymphoedema
- tissue inflammation
- abscesses
- ulcers
- cellulitis

These problems can lead to injecting in the groin and neck, resulting in:

- deep venous thrombosis
- large vessel stenosis
- pseudoaneurysm with high risk of massive haemorrhage

Intra-arterial injection can cause additional problems:

- distal limb ischaemia
- gangrene
- compartment syndrome
- rhabdomyolysis
- renal failure

Box

Ways to say no to requests for benzodiazepines

1. Be aware that 'doctor shoppers' tend to present as 'drop ins'. They will often come at the end of a busy surgery and say, 'I won't take up much of your time Doc', or 'I know you're busy, this won't take long'.
2. Put a notice on the surgery notice board stating that you do not prescribe benzodiazepines (or other drugs of dependence).
3. Explain early in the consultation that you do not prescribe benzodiazepines.
4. Politely but firmly repeat your message: 'I'm sorry but I am unable to prescribe benzodiazepines'.
5. Injecting drug users will sometimes use benzodiazepines for heroin withdrawal; however, this is not the treatment of choice. Have information ready about appropriate treatment and referral for drug and alcohol issues, including selective drug withdrawal, detoxification and rehabilitation.
6. Have information available about healthy sleeping and sleep hygiene.
7. Let the patient know that you are willing to help them with any health problems and that you are concerned about their potentially hazardous use of benzodiazepines.
8. Some injecting drug users will try to manipulate the practitioner with statements such as 'I'll have to go and use heroin' or 'I'll have a fit, if I withdraw', the inference being that it will be all the doctor's fault as they are unwilling to help. It is important that doctors are clear in their own minds that they are in no way responsible for that person's choice and that in this instance they have a duty of care **not** to prescribe benzodiazepines. Seek specialist advice if concerned about the risk of withdrawal fitting. If you feel physically threatened by the patient, do not hesitate to write a prescription, report the incident to the police and ban the individual from your practice.

Table 1

The United Kingdom experience

The UK faced similar problems with the injecting misuse of temazepam gelcaps in the early 1990s. In 1996 after education campaigns failed to adequately control the problem, gelcaps were removed from the National Health Service. Injecting drug users did not switch to injecting other benzodiazepines and the change resulted in an almost total disappearance in the injecting misuse of gelcaps and a consequent significant health benefit.

Changes in Australia

In mid-2002, in response to the concerns over misuse, the Pharmaceutical Benefits Advisory Committee rescheduled 10 mg temazepam gelcaps to require an authority prescription. However, in Kings Cross this did not result in a reduction in temazepam's injection and associated harms. In fact, if anything, there appeared to be an increase in misuse. Injecting drug users reported no difficulty obtaining gelcaps, either from doctors or from the street black market. Gelcaps (10 mg and 20 mg) remained widely available on private scripts for approximately $15–25 a script for 25–50 capsules. Each temazepam gelcap had a street black market value of about $5, making it a very lucrative and worthwhile prescription. The 20 mg dosage appeared to be the most popular, although it was not available on the Pharmaceutical Benefits Scheme and required a private prescription. Alphapharm withdrew its temazepam capsule in February 2004, however this made little difference to the use and availability of the more popular brands of temazepam.

In March 2004, Sigma withdrew its capsules from the market. This has completely removed the gelcap formulation from Australia and as a consequence will have positive benefits for injecting drug users. Although temazepam capsules have been withdrawn, doctors need to be careful when prescribing benzodiazepines or other drugs of dependence. They need strategies to help them refuse demands for a prescription (see box).

Conclusion

The harmful effects of injecting the contents of temazepam gelcaps led to the withdrawal of this product from the Australian market. Doctors still ought to be vigilant to detect harm associated with the misuse of benzodiazepines and carefully consider the need to prescribe drugs with a risk of dependence, particularly to anyone who could be an injecting drug user or be in contact with injecting drug users.

References

1. Salonen M, Aantaa E, Aaltonen L, Hovi-Viander M, Kanto J. A comparison of the soft gelatin capsule and the tablet form of temazepam. Acta Pharmacol Toxicol 1986;58:49-54.
2. Stark C, Sykes R, Mullin P. Temazepam abuse. Lancet 1987;2:802-3.
3. Vella EJ, Edwards CW. Death from pulmonary microembolisation after intravenous injection of temazepam. Br Med J 1993;307:26.
4. Aitken CK, Higgs P. Severe vein damage caused by temazepam injecting. Aust N Z J Public Health 2002;26:79.
5. Darke SG, Ross JE, Hall WD. Benzodiazepine use among injecting heroin users. Med J Aust 1995;162:645-7.
6. Sunjic S, Howard J. 'Non injectables': methadone syrup and benzodiazepine injection by methadone-maintained clients. Drug Alcohol Rev 1996;15:245-50.
7. Darke S, Topp L, Ross J. The injection of methadone and benzodiazepines among Sydney injecting drug users 1996-2000: 5-year monitoring of trends from the Illicit Drug Reporting System. Drug Alcohol Rev 2002;21:27-32.
8. Weatherburn D, Jones C, Freeman K, Makkai T. The Australian heroin drought and its implications for drug policy. Crime and justice bulletin. Sydney: NSW Bureau of Crime Statistics and Research; 2001 Oct. Report No.: 59.

Conflict of interest: none declared

Medicines Australia Code of Conduct: breaches

Medicines Australia (formerly the Australian Pharmaceutical Manufacturers Association) has a code of conduct to guide the promotion of prescription drugs in Australia.[1] The latest edition of the Code of Conduct states that Medicines Australia will provide information on its web site about complaints involving activities directed towards members of the public.[2] It is pleasing to report that Medicines Australia has expanded its external reporting by posting details of **all** the complaints the Code of Conduct Committee resolved between July and December 2003.[3]

In this six-month period 21 complaints were resolved. Most of the complaints were made by rival companies, but four were made by health professionals, and the Therapeutic Goods Administration made two. Four complaints were withdrawn and four complaints contained no breaches. This leaves 13 complaints where at least one breach was found (Table 1). Four companies appealed against being found in breach, but these appeals were not upheld.

References

1. Roughead EE. The Australian Pharmaceutical Manufacturers Association Code of Conduct: guiding the promotion of prescription medicines. Aust Prescr 1999;22:78-80.
2. Medicines Australia. Code of Conduct. 14th ed. Canberra: Medicines Australia; 2003.
3. http://www.medicinesaustralia.com.au/public/cocCommittee-Outcomes-July-Dec03.pdf [cited 2004 May 14]

Table 1

Breaches of the Code of Conduct July–December 2003 [3]

Company	Drug involved in complaint		Sanction imposed by Code of Conduct Committee
	Brand name	Generic name	
Aventis	Actonel	risedronate	Withdrawal of promotional material. Corrective letter. $25 000 fine.
Bayer and GlaxoSmithKline	Levitra	vardenafil	Withdrawal of promotional material.
Eli Lilly	Cialis	tadalafil	Withdrawal of promotional material. Corrective letter. Changes to web site.
Lundbeck	Ebixa	memantine	$15 000 fine.
	Media release		
Merck Sharp & Dohme	Fosamax	alendronate	Withdrawal of promotional material.
	Zocor	simvastatin	Withdrawal of promotional material. $10 000 fine.
	Zocor	simvastatin	Withdrawal of promotional material. Corrective advertisement and letter.
Novartis	Famvir	famciclovir	Withdrawal of promotional material. $10 000 fine.
Pfizer	Lipitor	atorvastatin	Withdrawal of promotional material.
	Somac	pantoprazole	Withdrawal of promotional material. Corrective advertisement.
Roche	Pegasys	peginterferon alfa-2a	Withdrawal of promotional material.
	Trade display		
Servier	Coversyl	perindopril	Withdrawal of promotional material. $30 000 fine.
	Display of materials previously in breach		
Wyeth	Efexor	venlafaxine	Withdrawal of promotional material. Corrective e-mail.
	Internet publication		

Glucosamine for osteoarthritis of the knee

Geoff McColl, Associate Professor, Centre for Rheumatic Diseases and Department of Medicine, Royal Melbourne Hospital, Melbourne

Summary

Glucosamine is a normal constituent of the proteoglycans found in joint cartilage and synovial fluid. It has been recommended for many years by practitioners of complementary medicine for the treatment of osteoarthritis. Clinical trials have now shown that the use of oral glucosamine sulphate 1.5 g daily in patients with osteoarthritis of the knee results in a significant reduction in joint pain and an improvement in joint function. In addition, glucosamine appears to reduce the loss of cartilage in the knee joint over at least a three-year period, particularly in those with milder radiological osteoarthritis. It would therefore seem reasonable to recommend a trial of glucosamine in patients with symptomatic osteoarthritis of the knee.

Key words: arthritis, complementary medicine.

(Aust Prescr 2004;27:61–3)

Introduction

Osteoarthritis is the commonest form of arthritis and often results in significant disability. The management of osteoarthritis involves both pharmacological and non-pharmacological interventions to control pain and loss of function.[1] The drugs used to treat osteoarthritis can be classified as symptom-modifying (drugs that improve pain and joint function) or structure-modifying (drugs that alter the progression of joint damage, in particular cartilage loss). Symptom-modifying drugs include analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). It is controversial whether any substance fulfils the criteria for structure-modification, but two randomised controlled trials[2,3] suggest that the first may be glucosamine sulphate.

For more than 20 years, practitioners of complementary medicine have used glucosamine to treat patients with osteoarthritis. Their approach was further popularised by the publication of a book optimistically titled 'The arthritis cure' in the 1990s.[4] This book presented many excellent strategies for arthritis self-management, but several chapters discussing the use of glucosamine and a 'sister' preparation chondroitin were met with considerable scepticism by the traditional medical community.

In the 1990s multiple, small, variable quality studies were performed, mainly in Europe, to test the efficacy of glucosamine and chondroitin in patients with various types of osteoarthritis. These studies were evaluated in a meta-analysis in 2000.[5] The authors of this review of 15 studies concluded that 'trials of glucosamine and chondroitin preparations for osteoarthritis symptoms demonstrate a moderate to large effect, but quality issues and likely publication bias suggest that these effects are exaggerated. Nevertheless, some degree of efficacy appears probable for these preparations.'

Pathophysiology

Glucosamine sulphate is a derivative of the naturally occurring aminomonosaccharide glucosamine, a constituent of the glycosaminoglycans chains in aggrecan and other proteoglycans found in the synovial fluid and cartilage of joints. Aggrecan and other proteoglycans trap water into the matrix of cartilage providing it with the deformable resilience which is necessary for its function. In the early phases of osteoarthritis there is an increase in the production of structural molecules such as aggrecan and collagen, but this appears to be more than matched by an increase in their catabolism by proteases under the influence of cytokines. *In vitro*, the addition of glucosamine to chondrocyte cultures increases aggrecan synthesis. Whether this observation explains the apparent efficacy of glucosamine is currently unknown.

Pharmacology

Although glucosamine has been given parenterally, it is usually taken by mouth. Glucosamine sulphate is well absorbed orally but undergoes substantial first-pass metabolism. The half-life of one preparation of glucosamine (the one used in European clinical trials[2,3]) is 58 hours and it is distributed to liver, kidney and other tissues including the articular cartilage. Pharmacokinetic studies have suggested that glucosamine is generally a substrate for the synthesis of mucopolysaccharides rather than a source of energy. There is a latency of four to eight weeks before the therapeutic effect emerges.

In animal models of diabetes glucosamine increases insulin resistance through a mechanism that is not well understood. A concern with the use of glucosamine in the treatment of patients with osteoarthritis of the knee (a population which statistically has higher body mass indices (BMIs) than the community average) is a further increase in their insulin resistance. In both of the clinical trials of glucosamine patients with a high BMI were excluded.[2,3] It is therefore difficult to conclude that an increase in insulin resistance does not occur in humans.

Efficacy of glucosamine for osteoarthritis of the knee

The European randomised, controlled, double-blind trials took place in Belgium and the Czech Republic. They compared glucosamine sulphate 1.5 g daily to placebo for three years in patients with osteoarthritis of the knee. Both trials are admirable because they evaluated the efficacy of glucosamine in a rigorous way and over a period longer than almost all previous randomised studies of patients with osteoarthritis, particularly studies of NSAIDs which have been notoriously short. The trials are also notable because structure-modification was the primary end-point rather than symptom-modification, which was a secondary end-point. Both trials were sponsored by the Rotta Research Laboratorium and used that company's formulation of glucosamine sulphate. This formulation may differ from those available in Australia.

Belgian trial [2]

This trial screened 355 patients and enrolled 212 (76% women) of whom 106 received placebo and 106 received glucosamine sulphate for three years. Patients with BMIs greater than 30 kg/m^2 were excluded and thus the mean BMI of the group was 27.5 kg/m^2. The majority of the patients (70%) had mild osteoarthritic changes (Kellgren and Lawrence grade II[6]) on baseline X-rays. At the completion of the study, 71 remained in the placebo group and 68 in the glucosamine group. Most withdrawals were due to adverse events or being lost to follow-up.

The primary end-point was change in the joint space width of the narrowest medial tibiofemoral joint compartment. The main symptomatic secondary end-point was the WOMAC (Western Ontario and McMaster Universities Arthritis Index), a validated osteoarthritis outcome measure that evaluates pain, stiffness and limitation of function.

An intent-to-treat analysis, using a last observation carried forward approach, showed a significantly greater decrease in joint space width in the placebo group. After three years the joint space width appeared not to have significantly deteriorated in the patients taking glucosamine. If those patients who completed the study were analysed separately (a per protocol analysis), the mean joint space was reduced by 0.31 mm in the placebo group and increased by 0.07 mm in the glucosamine group. In a subsequent analysis of the data the authors found that those with the least severe osteoarthritis at baseline benefited the most from the use of glucosamine. Glucosamine had little effect in patients with the most severe radiological osteoarthritis.

The symptomatic response to glucosamine was also positive. There was a reduction (improvement) of the total WOMAC by 11.7% in the glucosamine group and an increase (worsening) of 9.8% in the placebo group. The pain and function, but not stiffness, subscales of the WOMAC were also significantly improved by glucosamine. There was a poor correlation between structural and symptomatic responses, with some of the patients with the worst radiological osteoarthritis having a significant symptomatic response.

Czech trial [3]

This study screened 385 patients and enrolled 202 (77% women) of whom 101 received placebo and 101 received glucosamine sulphate for three years. Patients with BMIs greater than 27 kg/m^2 were excluded and this reduced the mean BMI of the study population to a nearly normal level. Nearly 50% of the patients had X-rays showing the more severe Kellgren grade III changes. At the completion of the study 55 remained in the placebo group and 66 in the glucosamine group. Most of the withdrawals were due to adverse events or by 'free choice'.

The primary end-point was change in the joint space width of the narrowest medial tibiofemoral joint compartment after three years. The symptomatic secondary end-points were the Lesquesne index (another validated outcome measure for osteoarthritis of the knee) and the WOMAC. Joint space width remained relatively static during the study in the patients taking glucosamine and worsened in the patients taking placebo. The measures of symptomatic response were improved in both the groups, but the patients who took glucosamine improved significantly more than the placebo group.

Safety of glucosamine

The proportion of patients who dropped out of the trials was similar in the placebo and glucosamine groups. There were no significant differences between the glucosamine and placebo-treated patients in the frequency of adverse events. The most frequently reported adverse effect was abdominal pain or nausea. Rashes were uncommon. Routine blood tests were not affected by treatment. In the Belgian trial fasting blood glucose was not increased in the patients taking glucosamine although it must be remembered that patients with high BMIs were excluded which may have reduced the risk of unmasking diabetes.

Glucosamine for osteoarthritis affecting other joints

Little evidence of good quality supports the use of glucosamine in the treatment of osteoarthritis affecting other joints. Small studies of temporomandibular joint pain and lumbar degenerative joint pain have revealed equivocal efficacy. Although it is tempting to extrapolate the results from the knee to osteoarthritis of other joints, this needs to be done with caution and could only be sanctioned on the grounds of the apparently low toxicity of glucosamine.

Conclusions

The two trials suggest that glucosamine sulphate 1.5 g orally daily has a substantial symptom- and structure-modifying effect in patients with mild to moderate osteoarthritis of the knee

and a relatively normal BMI. Whether glucosamine would be as effective or as safe in patients with higher BMIs is currently unknown. The evidence of effectiveness only extends for three years. It is also unclear whether the long-term structure-modifying effects of glucosamine will translate into more 'real' outcomes such as reduced functional decline or a delayed requirement for total knee replacement surgery. Despite these reservations, it would be reasonable to recommend a trial of glucosamine sulphate for the majority of patients with osteoarthritis of the knee, particularly early in the disease when you would normally consider paracetamol or NSAIDs. Prescribers need to advise patients to expect a latency of a month or two between onset of treatment and symptomatic response. Continuing analgesic therapy may be needed during this period. Caution should be exercised in the use of glucosamine in patients with diabetes mellitus.

References

1. American College of Rheumatology subcommittee on osteoarthritis guidelines. Recommendations for the medical management of osteoarthritis of the hip and the knee: 2000 update. Arthritis Rheum 2000;43:1905-15.
2. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001;357:251-6.
3. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162:2113-23.
4. Theodosakis J, Adderly B, Fox B. The arthritis cure: the medical miracle that can halt, reverse, and may even cure osteoarthritis. New York: St Martin's Press; 1997.
5. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA 2000;283:1469-75.
6. Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, et al. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. Osteoarthritis Cartilage 1996;4:217-43.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

1. The benefits of glucosamine are limited to patients with severe osteoarthritis of the knee.
2. Glucosamine has no effect on the radiological progression of osteoarthritis of the knee.

Web site review

AdWatch web site www.healthyskepticism.org/adwatch.asp

Ken Harvey, School of Public Health, La Trobe University, Melbourne

Healthy Skepticism was originally established in Australia in 1982 as the Medical Lobby for Appropriate Marketing (MaLAM). The organisation maintains a web site containing an excellent (and growing) collection of material about the techniques and impact of pharmaceutical promotion.

AdWatch is a new service established by Healthy Skepticism. It aims to critique particular pharmaceutical advertisements, focusing on both the promotional techniques and the information content. AdWatch comments on how well the claims made by the advertisement fit with the evidence and independent expert opinion. The analysis concludes by making general recommendations about the use of the drug promoted. A feedback form is provided for comments on the analysis.

Nexium (esomeprazole) from AstraZeneca was the first advertisement critiqued by AdWatch, in October 2003. Respondents' feedback was published in December 2003.

AdWatch has just commenced and inevitably there is room for improvement. The site could be improved by better linkage of its materials. In particular, the home page, 'Welcome to AdWatch', lacks the links to 'Introduction' contained on subsequent pages which explain the background to AdWatch. In addition, the home and subsequent pages lacked a link to 'Feedback about the AdWatch prototype' (found on the site map) which had useful correspondence with AstraZeneca staff about the prototype Nexium critique. I suggest that every AdWatch critique should offer the pharmaceutical company involved a space for their response, even if this may not always be forthcoming. AdWatch would provide additional value if it was linked to the National Prescribing Service (NPS) information service (RADAR) about drugs newly listed on the Pharmaceutical Benefits Scheme (PBS).[1]

Conclusion

Given the money spent on pharmaceutical promotion and its proven ability to influence drug use, AdWatch (and Healthy Skepticism) provide a unique and valuable corrective service. AdWatch is free and should be part of all health practitioners' continuing education strategies. The NPS should at least add AdWatch to the list of useful links on its web site.

Reference

1. http://www.npsradar.org.au

Abnormal haematology results in children

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Summary

Care must be taken when interpreting haematology results in children. They have different physiology from adults so the normal ranges for results differ. The results also vary according to the age of the child. To ensure children are not misdiagnosed or incorrectly investigated, it is important to know if the reporting laboratory has established age-specific reference ranges for children.

Key words: haemoglobin, blood coagulation factors, partial thromboplastin time, prothrombin time.

(Aust Prescr 2004;27:64–6)

Introduction

Pathology tests are an integral part of current medical practice. The accurate and appropriate interpretation of these tests is essential when they are being used for diagnosis or disease monitoring. The critical issues include:

- the choice of the correct test for the clinical situation
- an understanding of the 'normal' or expected results of the test
- an understanding of all of the potential causes of an abnormal result, including spurious causes
- the relative 'weight' that should be given to an abnormal result given the full clinical context.

Children add an additional layer of complexity to each of these issues. For example, issues related to sample collection and the use of capillary blood are particularly relevant causes of spurious results. Perhaps the most misunderstood issue is the concept of 'normal' in different age groups. Countless children are misdiagnosed or over-investigated because of a lack of understanding that they are not just 'little adults', but are physiologically different in many respects. This lack of understanding often extends to the laboratory reporting the results. The clinician may be led astray by reports that would be correct for adult patients, but are non-contributory or wrong in children. Nowhere is this more obvious than within haematology. Developmental or age-related changes in haemopoiesis and haemostasis have significant effects on the interpretation of some common pathology tests.

Full blood examination

In the full blood examination the greatest numerical difference between children and adults is seen in the white cell count and differential. The white cell count is significantly higher in children of all ages, until mid-adolescence where it approximates adult counts.

Neutrophils

A high neutrophil count is commonly seen, particularly in neonates. The neutrophil count may be up to 14 x 10^9/L in a normal neonate.[1] These 'normal' differences must be considered, for example in the diagnosis of bacterial infection. Other considerations are the potential response of the child to sepsis (very sick children may have neutropenia) and the effects of concomitant therapies such as steroids in croup or asthma. Features such as neutrophil vacuolation, toxic granulation or left shift with increased band forms are important determinants in the interpretation of neutrophil counts in children.

Lymphocytes

Compared to adults, a relative lymphocytosis is common in normal children. Lymphocyte counts up to 11 x 10^9/L are normal in children under twelve months and elevated counts persist until mid-adolescence.[1] Results that may suggest lymphoproliferative disorders in adult patients, are usually either normal, or reflect common clinical and subclinical viral infections in children. Less commonly understood is the fact that morphologically normal lymphocytes in young infants often appear atypical, or even blast-like. Experience with paediatric blood films is required to avoid the unnecessary suggestion of leukaemia in many children, or the overdiagnosis of specific viral infections associated with atypical lymphocytes.

Erythrocytes and haemoglobin

Red cell parameters vary significantly between the various age ranges. Relative polycythaemia is normal in the early days of life in both the term and premature newborn. The normal haemoglobin concentration ranges from 13.5 g/dL to 22.0 g/dL in the first weeks of life. This occurs in response to high fetal erythropoietin levels stimulated by the relative hypoxia experienced *in utero*.

The haemoglobin concentration in normal infants declines after birth to reach the physiological nadir at approximately

eight weeks of age (normal range 9.0–14.0 g/dL). Adverse neonatal events, prematurity and haemolysis (due, for example, to maternal-fetal ABO incompatibility) may impact significantly on the rate and extent of this decline. The causes of the decline include accelerated red cell loss around the time of delivery, reduced survival of neonatal red cells (approximately 90 days v. 120 days) and erythropoietin deficiency as a result of negative feedback from increased oxygenation after the normal neonatal circulation is established. The fall in haemoglobin reactivates erythropoietin production, and the normal feedback mechanism that persists for the remainder of life is established.[2]

Red cell size follows a similar pattern to the haemoglobin concentration. Fetal red blood cells are macrocytic relative to adults, with the normal range of mean cell volume (MCV) at birth 100–120 fl. This reduces to 85–110 fl by one month and 70–90 fl by six months, before increasing again from early adolescence to reach normal adult values (80–97 fl) by late adolescence.[2] The initial reduction in MCV occurs as the macrocytic fetal red cells are replaced during the first months of life.

Deviations in red cell size may indicate significant disease in children. Macrocytosis is commonly due to hepatic dysfunction, anticonvulsant therapy, hypothyroidism or B_{12}/folate deficiency, and is an early marker of significant bone marrow disorders such as aplastic anaemia. A reduced MCV suggests conditions such as iron deficiency or a thalassaemia syndrome. While iron studies and haemoglobinopathy screening are warranted in adults with an MCV in the high 70s fl, this result is normal for the majority of children through the years of mid-childhood. In the absence of prematurity or substantial blood loss, microcytosis in the first six months of life almost always indicates an α-thalassaemia carrier. Normal fetal iron stores are sufficient during this time, irrespective of diet, and β-thalassaemia carriers do not develop microcytosis until after haemoglobin chain switching (from fetal to adult haemoglobin) occurs at around six months.

Coagulation studies

Developmental haemostasis can produce significant discrepancies between normal ranges of coagulation studies, such as the prothrombin time and activated partial thromboplastin time (APTT), depending on age and prematurity.[3] Table 1 shows the normal ranges for APTT in our laboratory compared to the age-related reference ranges published in the literature. The impact of different reagent and analyser systems is obvious.

Most laboratories do not have the resources required to establish age-appropriate reference ranges, however, until such systems are put in place, over-investigation of normal children whose coagulation results are labelled abnormal will continue. The clinical dilemma is that significant conditions such as Von Willebrand's disease may exist in children with a mildly prolonged APTT.

Often the clinical rationale for coagulation testing in children relates to 'abnormal' bruising that may raise questions of non-accidental injury. The interpretation of results then becomes a matter for legal debate as well as clinical management. Simple calculations show that in our laboratory, if we used the adult reference range, approximately 30% of all 1–10 year-olds would be labelled as abnormal and further investigations would ensue. The direct costs of these further investigations (such as repeat APTT, intrinsic factor assays, and Von Willebrand's screening) amounts to hundreds of dollars per child.[4] This does not consider the indirect costs such as cancelled surgery, referral for specialist review, and missed work (parents) and school to attend hospital appointments.

There is therefore a considerable imperative for all laboratories performing coagulation studies in children to report the results accurately based on age-related reference ranges that are specific to their analyser and reagent systems. The clinician must also be circumspect in the interpretation of all coagulation studies in children.

Abnormalities of coagulation testing have different interpretations in children and adults. For example, a prolonged APTT that fails to correct on mixing studies (mixing studies usually involve a one-to-one mix of patient plasma with normal plasma before APTT testing) is commonly due to a so-called lupus anticoagulant. These non-specific antiphospholipid antibodies can be associated with autoimmune disease in

Table 1

Normal ranges for activated partial thromboplastin time according to age

APTT (in seconds)	Age (years)				
	< 1	1–5	6–10	11–16	Adults
* Laboratory data[5] mean (range)	38 (26–50)	37 (30–45)	37 (29–46)	37 (31–44)	33 (28–38)
Published data[3,6,7] mean (range)	35.5 (28.1–42.9)	30 (24–36)	31 (26–36)	32 (26–37)	33 (27–40)

* As performed by the Royal Children's Hospital Laboratory on the STA-compact analyser with STAGO reagent systems (Diagnostica STAGO, France)

APTT activated partial thromboplastin time

adults, and in particular thrombotic manifestations. While the same is true in children, they are far more frequently a transient phenomenon seen after viral illness and in these circumstances are rarely associated with significant pathology.

Conclusion

Misinterpretation of haematology tests in children is common. Specific issues need to be considered to ensure appropriate interpretation of results. In particular, an understanding of 'normal' for different age groups is critical to both full blood examination and coagulation studies. Many laboratories within Australia do not report these parameters appropriately, and the clinician must be aware of this to guide subsequent management and investigation.

References

1. Expected hematologic values for term and preterm neonates. In: Christensen RD, editor. Hematologic problems of the neonate. Philadelphia: W.B. Saunders Co.; 2000. ch 7.
2. Smith, H. Diagnosis in paediatric haematology. New York: Churchill Livingstone; 1996. ch 1, 8.
3. Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. Blood 1992;80:1998-2005.
4. Ignjatovic V, Barnes C, Newall F, Campbell J, Savoia H, Monagle P. The importance of age appropriate haemostasis reference ranges [poster, abstract BO55, presented at HSANZ meeting; 2002; Adelaide, Australia].
5. Monagle P, Ignjatovic V, Barnes C, Newall F, Campbell J, Savoia H, et al. Reference ranges for haemostatic parameters in children [poster, abstract P0076, presented at XIX ISTH Congress; 2003 Aug 10-14; Birmingham, UK]. J Thromb Haemost 2003;1(S1).
6. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, et al. Development of the human coagulation system in the full-term infant. Blood 1987;70:165-72.
7. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, et al. Development of the human coagulation system in the healthy premature infant. Blood 1988;72:1651-7.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 79)

3. Children bruise easily because they have a shorter partial thromboplastin time than adults do.
4. Microcytosis in a neonate is usually a sign of iron deficiency.

Book review

Statistics with common sense. David Kault. Westport (CT): Greenwood Publishing; 2003. 272 pages. Price $65 approx.*

John Attia, Senior Lecturer in Epidemiology, University of Newcastle, and Academic Consultant, John Hunter Hospital, Newcastle, NSW

This is a refreshing change from the standard textbook on statistics. Rather than presenting statistics as a dry mathematical endeavour with the objective authority of an oracle, the author casts it as a useful decision aid in the context of making subjective and complex judgements in medicine.

The particular strength of the book is the explanation of the conceptual framework surrounding the 'frequentist' school of statistics and hypothesis testing, given in chapters 1 and 6. For anyone who has ever wondered what a p-value or a 95% confidence interval **really** mean, this is the section to read. There is also a good introduction to Bayesian statistics.

The author takes an unorthodox approach to explaining the principles behind various statistical tests that, by and large, works well. In chapters 3, 4, 5, 8 and 9 the author communicates an intuitive understanding of the principles behind t-tests, chi-square, ANOVA, regression, and various non-parametric tests. This is challenging and demanding; although those who are math-phobic will not find this easy, the educated practitioner who is not afraid to tackle the text and follow the logic will be rewarded. In some cases though, the unorthodox approach does not quite succeed; I found myself confused by the order in which the various tests are presented, and the relation between them, for example regression and correlation are presented together in chapter 8. Chapter 7 presents an absolutely first-rate discussion of causality, one that every clinician reading papers should know.

The book is very readable; the author uses accessible examples that do not require a medical background and builds his explanation like a narrative. This is both a strength and a weakness, in that it makes it a little more difficult to use the book as a reference (although there is a good index). The author also provides a free statistics software program on his web site which is useful.

In summary, this book has much to recommend it, and although it is neither a quick nor simple read, it lives up to its title as an excellent synthesis of statistics and common sense, a rare book that will give the persistent reader a better understanding of the uses (and misuses!) of statistics.

* available from DA Information Services (03) 9210 7717 or e-mail service@dadirect.com

Thiazolidinediones – mechanisms of action

Jerry R. Greenfield, Endocrinologist and Postgraduate Research Fellow, and Donald J. Chisholm, Professor of Endocrinology, Diabetes and Obesity Research Program, Garvan Institute of Medical Research, and Department of Endocrinology, St Vincent's Hospital, Sydney

Summary

The thiazolidinediones (or 'glitazones') are a new class of drugs for the treatment of type 2 diabetes. They bind avidly to peroxisome proliferator-activated receptor gamma in adipocytes to promote adipogenesis and fatty acid uptake (in peripheral but not visceral fat). By reducing circulating fatty acid concentrations and lipid availability in liver and muscle, the drugs improve the patient's sensitivity to insulin. Thiazolidinediones favourably alter concentrations of the hormones secreted by adipocytes, particularly adiponectin. They increase total body fat and have mixed effects on circulating lipids.

Key words: hypoglycaemic drugs, insulin, diabetes, pioglitazone, rosiglitazone.

(Aust Prescr 2004;27:67–70)

Introduction

Despite the explosion in the prevalence of type 2 diabetes in the last 50 years, there has been a distinct lack of progress in the development of new therapies. Together with decreased insulin secretion, insulin resistance, or a reduction in the biological activity of endogenous insulin, is a key component in the development of type 2 diabetes and 'prediabetic' states, such as impaired glucose tolerance. As the thiazolidinediones (or 'glitazones') improve insulin sensitivity through actions which are completely different from those of other oral hypoglycaemic drugs, there has been a lot of interest in their potential role in type 2 diabetes.[1]

The development of the thiazolidinediones

The discovery of thiazolidinediones and a substantial amount of the early developmental work occurred in Japan. The first compound, ciglitazone, improved glycaemic control in animal models of insulin resistance, but its mechanism of action was poorly understood and toxicity prevented trials in humans. Other compounds were subsequently developed with less toxicity in animals, and two important findings led to a rapid increase in our understanding of their mode of action. These findings were that thiazolidinediones:

- bind avidly to peroxisome proliferator-activated receptor gamma (PPARγ)[2]
- improve insulin sensitivity in parallel with a major change in fat metabolism, including a substantial reduction in circulating free fatty acids.[3]

Three compounds – troglitazone, pioglitazone and rosiglitazone – have entered clinical practice and there has been a steadily increasing understanding of the multiple biological effects of these drugs. Unfortunately, troglitazone caused uncommon but serious liver toxicity, leading to its withdrawal from use. It seems likely that this toxicity was related to the vitamin E-like part of the molecule.[4] Hepatotoxicity does not seem to be associated with the other two compounds, but regular liver function tests are recommended.[1]

Molecular mechanisms of action

PPARγ is a member of a family of nuclear receptors. Another member of this class, peroxisome proliferator-activated receptor alpha (PPARα), is predominantly expressed in the liver and is thought to mediate the triglyceride lowering actions of fibrates.[5] PPARγ is expressed in many tissues, including colon, skeletal muscle, liver, heart and activated macrophages, but is most abundant in adipocytes.[1]

Thiazolidinediones are selective agonists of PPARγ. When activated by a ligand, such as a thiazolidinedione, PPARγ binds to the 9-*cis* retinoic acid receptor (RXR [retinoid X receptor]) to form a heterodimer.[1] This binds to DNA to regulate the genetic transcription and translation of a variety of proteins involved in cellular differentiation and glucose and lipid metabolism.[6]

Biological effects

Thiazolidinediones have several biological actions. Although the precise mechanism by which the thiazolidinediones improve insulin sensitivity is still not completely understood, a large part of their action is thought to be mediated by changes in body fat and its distribution.

Fat redistribution

One result of PPARγ activation is enhanced differentiation and proliferation of preadipocytes into mature fat cells, particularly

in non-visceral (peripheral or subcutaneous) fat depots. There is an upregulation of enzymes/transporters in adipocytes to facilitate their uptake of fatty acids (for example, increases in lipoprotein lipase, fatty-acid transporter 1 and glycerol kinase).[5]

It is notable, and probably important, that most of these consequences of PPARγ stimulation are **not** seen in visceral adipocytes, even though these cells have abundant PPARγ receptors. Visceral adipocytes are also metabolically quite different to peripheral adipocytes in other ways, for example they are less responsive to insulin and more responsive to catecholamines. Increased fatty acid storage in subcutaneous adipocytes results in a 'lipid-steal' phenomenon, leading to lower circulating fatty acids and reduced concentrations of triglycerides in muscle and liver (Fig. 1).[1,2] Studies in animals and humans have shown that thiazolidinediones only improve insulin action (and glycaemic control in diabetes) in the presence of insulin resistance.[3] This may be explained by the fact that the effects of these drugs on lipid redistribution are only beneficial if there is excess tissue lipid availability. The 'lipid-steal' effect of thiazolidinediones may therefore be a major contributor to improved insulin action in muscle (enhanced glucose utilisation) and liver (reduced hepatic glucose output), as the direct effects of PPARγ stimulation in muscle and liver are unclear. The potential role of the thiazolidinediones in reducing hepatic lipid content in non-alcoholic steatohepatitis is under investigation.

The thiazolidinediones do not increase insulin secretion. On the contrary, thiazolidinediones reduce insulin levels acutely, which may be a consequence of improved insulin sensitivity and/or reduced circulating fatty acids (as fatty acids stimulate insulin secretion). In the longer term, thiazolidinediones arrest the decline in β-cell function that occurs in type 2 diabetes, perhaps by protecting the β-cell from lipotoxicity.[7] The thiazolidinediones are of no use in type 1 diabetes or in the occasional lean insulin-deficient (but insulin-sensitive) patient with type 2 diabetes.

Adipokines and transporters

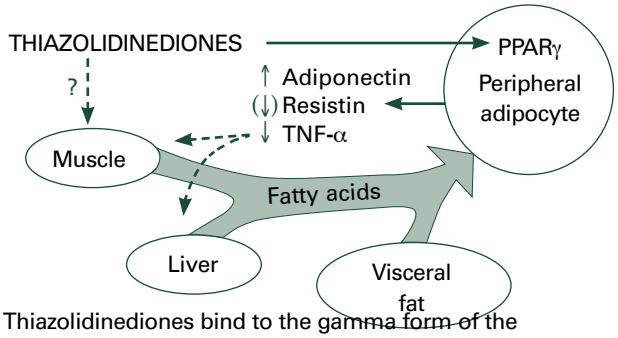
In addition to promoting adipogenesis and fatty acid uptake, thiazolidinediones are thought to improve insulin sensitivity by altering hormone production by adipocytes. Adipocytes secrete a number of important hormones, referred to as 'adipokines', including leptin, adiponectin, resistin and tumour necrosis factor-α (TNF-α).[6] The thiazolidinediones, again via PPARγ activation, substantially increase the production of adiponectin (which has been shown to increase fat oxidation, improve insulin action and to have anti-atherogenic properties). They also reduce the secretion of substances which impair insulin action such as TNF-α and, possibly, resistin (Fig. 1).[2,4]

There has been an interesting discussion about the degree to which the improved insulin response induced by thiazolidinediones is mediated by increased glucose processing molecules (such as the insulin regulated glucose transporter, GLUT 4, and pyruvate dehydrogenase activity) in adipocytes.[5] As adipocytes only account for a small component of insulin-induced glucose disposal, it seems likely that the effects of thiazolidinediones on these glucose handling proteins are not a major component of their activity.

Other biological effects

The effect of the thiazolidinediones on lipid concentrations is complex (Table 1). HDL cholesterol concentrations tend to

Mechanism of action of thiazolidinediones



Thiazolidinediones bind to the gamma form of the peroxisome proliferator-activated receptor (PPARγ). This stimulates peripheral adipocytes to increase their uptake of free fatty acids, which leads to reductions in the fat stored in muscle, liver and visceral fat deposits. The thiazolidinediones also lead to an increase in the secretion of adiponectin and a decrease in the production of resistin and tumour necrosis factor α (TNF-α). It is unknown if thiazolidinediones have direct effects on muscle or liver.

Table 1

Additional biological effects of the thiazolidinediones [7]

Increased HDL cholesterol concentrations
Increased LDL cholesterol concentrations
Increased LDL cholesterol particle size
Reduced triglyceride concentrations (particularly pioglitazone)
Small reduction in blood pressure
Reduced incidence of microalbuminuria
Decrease in plasminogen activator inhibitor-1 and fibrinogen
Vasorelaxation
Increase in vascular reactivity
Anti-inflammatory effects

All of these effects, except for increased LDL cholesterol concentrations, would be regarded as potentially beneficial in regard to the metabolic syndrome and cardiovascular disease.

Fig. 1

increase while triglyceride concentrations decrease.[1] Although LDL cholesterol concentrations may increase initially, this effect lessens over time and particles are now larger and more buoyant.[2,4] The outcomes of ongoing large clinical trials may clarify the effect of thiazolidinediones on cardiovascular risk. Pioglitazone has some PPARα activity, which may account for the data suggesting a more favourable effect on triglyceride and LDL cholesterol levels.[7]

Most of the other biological effects of the thiazolidinediones are potentially beneficial and related to improvements in parameters of the insulin resistance syndrome (Table 1). Many of these effects are probably due to changes in lipid metabolism or adipokines, although detailed mechanisms are not fully understood. These changes have generally only been recorded in animal or human models of insulin resistance. Another reported effect, which may not be mediated by PPARγ, is a degree of anti-inflammatory activity and reduction in macrophage function.[2] Limited evidence also suggests that the thiazolidinediones may improve insulin resistance and ovulatory function in women with polycystic ovary syndrome.[7]

Mechanisms of adverse effects

Given the effect of the thiazolidinediones on adipocyte differentiation and proliferation, particularly in peripheral adipocytes, it is not surprising that an adverse effect of thiazolidinedione treatment is a gain in weight and peripheral fat mass. In fact, there tends to be a correlation between increasing peripheral fat and clinical improvement in insulin sensitivity and glycaemia in type 2 diabetes. On the other hand, visceral fat, which appears far more metabolically 'harmful' than peripheral fat, is not increased and may, in fact, decrease with thiazolidinedione therapy.[2]

An adverse effect, which may preclude the use of the thiazolidinediones in patients with moderate to severe cardiac failure, is fluid retention. This is an important class effect, which may result in peripheral oedema, particularly in patients taking concomitant insulin therapy (which may itself cause some increase in interstitial fluid). An increase in plasma volume results in a small drop in haemoglobin concentrations due to haemodilution. This is rarely clinically significant.

Pharmacokinetics and drug interactions

The thiazolidinediones are rapidly absorbed and reach peak concentrations within a few hours.[4] Steady-state is usually reached within one week, but perhaps because of the importance of fat redistribution, the full benefit may take 4–12 weeks to become evident. Rosiglitazone and pioglitazone are strongly protein bound in the circulation, predominantly to albumin.[4] No significant drug interactions have been reported with the thiazolidinediones, but it should be noted that in combination with the sulfonylureas, hypoglycaemia may occur due to the combination of enhanced insulin sensitivity (thiazolidinediones) and enhanced insulin secretion (sulfonylureas). Thiazolidinediones are metabolised by cytochrome P450 2C8 (and by CYP3A4 for pioglitazone), but at conventional doses apparently do not affect the activity of those enzymes. Caution should still be exercised when using thiazolidinediones in combination with drugs metabolised by these enzymes.

Conclusion

The discovery and development of the thiazolidinediones represent a significant advance in our understanding of the aetiology of insulin resistance, particularly in relation to adipocyte biology. The thiazolidinediones are a new mode of therapy for type 2 diabetes. Their action, in large part, is mediated by activation of PPARγ and involves redistribution of surplus fatty acids to peripheral fat. This reduces fatty acid availability in the circulation as well as in liver and muscle – thus improving insulin sensitivity. A second aspect of their action is the modification of adipokine secretion.

References

1. Schoonjans K, Auwerx J. Thiazolidinediones: an update. Lancet 2000;355:1008-10.
2. Gurnell M, Savage DB, Chatterjee VK, O'Rahilly S. The metabolic syndrome: peroxisome proliferator-activated receptor gamma and its therapeutic modulation. J Clin Endocrinol Metab 2003;88:2412-21.
3. Oakes ND, Kennedy CJ, Jenkins AB, Laybutt DR, Chisholm DJ, Kraegen EW. A new antidiabetic agent, BRL 49653, reduces lipid availability and improves insulin action and glucoregulation in the rat. Diabetes 1994;43:1203-10.
4. Mudaliar S, Henry RR. New oral therapies for type 2 diabetes mellitus: The glitazones or insulin sensitizers. Annu Rev Med 2001;52:239-57.
5. Lee CH, Olson P, Evans RM. Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. Endocrinology 2003;144:2201-7.
6. Furnsinn C, Waldhausl W. Thiazolidinediones: metabolic actions in vitro. Diabetologia 2002;45:1211-23.
7. Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA. Nonhypoglycemic effects of thiazolidinediones [published erratum appears in Ann Intern Med 2001;135:307]. Ann Intern Med 2001;134:61-71.

Further reading

O'Moore-Sullivan TM, Prins JB. Thiazolidinediones and type 2 diabetes: new drugs for an old disease [published erratum appears in Med J Aust 2002;177:396]. Med J Aust 2002;176:381-6.

Weissman P. Reappraisal of the pharmacologic approach to treatment of type 2 diabetes mellitus. Am J Cardiol 2002;90 (Suppl 5A):42G-50G.

Professor Chisholm has received research funding for preclinical studies on thiazolidinediones and has given lectures for and participated in advisory boards for both Eli Lilly and GlaxoSmithKline, marketers of pioglitazone and rosiglitazone. He has no beneficial interest and does not receive consultancy payments from either company other than for lectures and advisory board meetings.

Self-test questions

The following statements are either true or false (answers on page 79)

5. Treatment with thiazolidinediones leads to weight reduction in patients with type 2 diabetes.
6. Haemoglobin concentrations may fall during treatment with thiazolidinediones.

Experimental and clinical pharmacology

Clinical indications for thiazolidinediones

Richard J. MacIsaac, Endocrinologist, and George Jerums, Director of Endocrinology, Endocrine Unit, Austin Health and Professorial Fellow, Department of Medicine, University of Melbourne, Melbourne

Summary

Undertreatment of hyperglycaemia in type 2 diabetes is a major therapeutic problem. This is partly because reduced insulin sensitivity and beta cell failure become resistant to current therapies. The thiazolidinediones are a new class of drugs that improve insulin sensitivity. However, large-scale clinical trials are needed to assess their clinical roles and whether they have microvascular protective effects beyond those associated with lowering blood glucose. Trials with clinical end-points are also required to determine if thiazolidinediones reduce macrovascular disease. Thiazolidinediones can cause delayed-onset hypoglycaemia, especially in combination with other oral hypoglycaemic drugs, weight gain and fluid retention. The fluid retention may precipitate heart failure so careful monitoring of weight gain and peripheral oedema is required.

Key words: diabetes, hypoglycaemic drugs, pioglitazone, rosiglitazone.

(Aust Prescr 2004;27:70–4)

Introduction

Lifestyle changes including weight loss and increased activity are the primary recommendations for treatment of type 2 diabetes. However, because of the progressive nature of the disease, the treatment of type 2 diabetes usually requires the stepwise introduction of oral hypoglycaemic drugs followed by insulin.[1] Despite this approach less than 10% of patients with type 2 diabetes maintain their concentration of glycated haemoglobin (HbA1c) below 7%, which is still about two standard deviations above the upper limit of the normal range. The reasons for this are complex and include factors relating to organisations, doctors, patients and deficiencies in drug efficacy. These may arise from a delay in the translation of new guidelines into clinical practice, patient resistance to starting insulin and secondary failure of existing oral hypoglycaemic drugs.

The thiazolidinediones are a recent addition to the list of hypoglycaemic drugs (Table 1). Rosiglitazone and pioglitazone are now listed on the Australian Pharmaceutical Benefits Scheme (PBS) for the treatment of type 2 diabetes.

Mechanism of action

Thiazolidinediones do not stimulate insulin secretion. They act by improving insulin sensitivity via activation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ). There is an increase in glucose utilisation by skeletal muscle and fat cells, increased uptake of free fatty acids and reduced lipolysis by fat cells, and to possibly a lesser extent a reduction in hepatic gluconeogenesis. For fat cells the ratio of adipogenesis to apoptosis is also differentially altered favouring apoptosis of larger insulin-resistant cells and the proliferation of smaller insulin-sensitive adipocytes. This is accompanied by a shift in the distribution of fat from central to peripheral depots.

Glycaemic control – response, onset and duration of action

Thiazolidinediones progressively reduce concentrations of blood glucose. The HbA1c falls by 0.5–1.5% over one to three months. Maximal glucose-lowering effects may not be seen for up to three months and therefore dose adjustments prior to this time should be undertaken with caution.

The hypoglycaemic effects of pioglitazone 15–45 mg daily are similar to those of rosiglitazone 4–8 mg daily. The thiazolidinediones produce a wider response in HbA1c concentrations in comparison to other oral hypoglycaemic drugs. It is not possible to differentiate 'good' from 'bad' responders prospectively but, in general, the reduction in HbA1c is greater when thiazolidinediones are used in combination with other drugs. There is also some evidence to suggest that obese patients respond better than those with a body mass index close to normal. Defining the proportion of patients who respond to a thiazolidinedione is a difficult question to answer because there is no clear definition of a 'responder'. The context of a response therefore could vary in the setting of mono-, dual or triple therapy, however, possibly up to 30% of patients may not respond with a decrease in HbA1c concentrations.

A major question is whether the glycaemic response to thiazolidinediones is maintained longer than with other oral hypoglycaemic drugs. So far, studies up to four years in duration have not shown a delayed increase in HbA1c. It will require at least another four years before it is clear whether or not secondary failure occurs with thiazolidinediones as it does with other oral hypoglycaemic drugs.

Adverse effects

The thiazolidinediones have effects in many different tissues. As only limited information is available on their long-term use, significant adverse effects may yet emerge. Monotherapy with thiazolidinediones is not associated with hypoglycaemia, but clinical hypoglycaemia has been reported when they are used in combination therapy. Hypoglycaemia may occur many weeks after starting a thiazolidinedione because of the slow onset of action.

Troglitazone, the first member of the class, was withdrawn as a consequence of liver failure. Hepatotoxicity has not been a problem with pioglitazone and rosiglitazone although regular monitoring of liver function is still recommended.

The main adverse effects of thiazolidinediones are weight gain of 1–4 kg after six months of treatment, fluid retention and dilutional anaemia. Increases in weight reflect fluid retention and an increase in peripheral fat mass (albeit with a concurrent decrease in central fat). The fluid retention may be due to increased endothelial cell permeability or a renal effect of thiazolidinediones, but a local vasodilatory action cannot be excluded. Oedema may occur more frequently in patients with a good glycaemic response to thiazolidinediones, especially those who are taking insulin. It is also more likely to be noticed in patients taking medications that promote oedema such as dihydropyridine calcium channel blockers. Thiazolidinediones can be used in patients with renal impairment as long as fluid overload is not an issue.

Heart failure

The most dangerous adverse effect of thiazolidinediones is fluid retention leading to congestive cardiac failure. Some degree of peripheral oedema occurs in 5–15% of patients and 2–3% develop cardiac failure. A recent retrospective cohort study has shown that the use of thiazolidinediones was associated with an approximately 70% increase in the relative risk of developing heart failure.[2] In that study, the adjusted estimated incidence of heart failure (defined as a hospitalisation or outpatient visit

Table 1

Comparison of oral hypoglycaemic drugs available in Australia

Drug class	Preparations available	Mechanism of action	Pharmaceutical Benefits Scheme listing
Thiazolidinediones	rosiglitazone pioglitazone	increase insulin sensitivity	authority required
Biguanides	metformin	reduce hepatic gluconeogenesis	unrestricted benefit
Sulfonylureas	glibenclamide gliclazide gliclazide MR glimepiride glipizide	increase pancreatic insulin secretion	unrestricted benefit
Meglitinides	repaglinide	increase pancreatic insulin secretion	not listed
α-glycosidase inhibitors	acarbose	delay absorption of complex carbohydrates	authority required

with a diagnosis of heart failure) was 8.2% for thiazolidinedione-treated patients and 5.3% for the control group after 40 months of exposure.

A joint consensus statement regarding thiazolidinedione use, fluid retention and heart failure has been released by the American Heart Association and the American Diabetes Association.[3] The following factors are associated with an increased risk of developing heart failure:

- history of heart failure (systolic or diastolic)
- history of prior myocardial infarction or symptomatic heart failure
- hypertension
- left ventricular hypertrophy
- significant aortic or mitral valve disease
- advanced age (over 70 years)
- long-standing diabetes (over 10 years)
- pre-existing oedema or current treatment with loop diuretics
- development of weight gain or oedema on thiazolidinedione therapy
- insulin co-administration
- chronic renal failure.

Thiazolidinediones are therefore contraindicated in patients with moderate to severe symptoms or signs of angina or heart failure during daily activities or at rest (New York Heart Association (NYHA) class III or IV cardiac functional status). For patients in the class I or II NYHA categories, thiazolidinediones can probably be prescribed with extreme caution. It is recommended that patients start with the lowest doses of thiazolidinediones and be carefully observed for fluid retention. The same caution should also apply to patients who do not have symptoms or signs of heart failure, but who have had an echocardiogram revealing impaired ventricular function.

Drug interactions

Pioglitazone is partially metabolised by cytochrome P450 3A4 and rosiglitazone is predominantly metabolised by P450 2C8. A number of drugs used in everyday clinical practice modulate the activity of the P450 3A4 enzyme and gemfibrozil has been reported to inhibit the P450 2C8 enzyme resulting in increased concentrations of rosiglitazone. However, no clinical syndromes have yet been reported as a result of drug interactions that could potentially alter the metabolism of the thiazolidinediones.

Clinical indications for the treatment of type 2 diabetes

In the absence of cost and regulatory considerations, thiazolidinediones could potentially be used in:

- monotherapy
- dual therapy with either a sulfonylurea or metformin
- triple therapy in combination with both a sulfonylurea and metformin
- combination with insulin.

Current PBS regulations do not allow all of these options.

Monotherapy

When used alone, pioglitazone and rosiglitazone are effective at reducing concentrations of HbA1c and fasting blood glucose in adults with type 2 diabetes. These effects are similar to those of other available oral hypoglycaemic agents.

Combined therapy with other oral drugs

The advantages of adding thiazolidinediones are mainly theoretical and include the preservation of β-cell function and hence secondary failure, and possibly cardiovascular protection. These effects remain to be rigorously tested in large prospective clinical studies.

For patients on monotherapy with either a sulfonylurea or metformin, the addition of a thiazolidinedione produces a further significant decrease in HbA1c and fasting blood glucose.[4] However, there is little evidence to suggest that this approach will provide better short-term glycaemic control than the combination of metformin and a sulfonylurea.

The use of thiazolidinediones under the PBS is limited to the combination with either metformin or a sulfonylurea. Patients must have an intolerance or contraindication to either metformin or a sulfonylurea to qualify for treatment with thiazolidinediones. As intolerance and contraindications are more common with metformin than with sulfonylureas, the main use of thiazolidinediones in Australia is likely to be in combination with a sulfonylurea.

In contrast to the PBS listing, the main use of thiazolidinediones so far in Australia has been in combination with both metformin and a sulfonylurea as part of schemes sponsored by the manufacturers of pioglitazone and rosiglitazone. This triple therapy has evolved for two reasons. Firstly, it is now common practice to combine metformin with a sulfonylurea at an early stage of treatment of diabetes and secondly, patients are reluctant to start insulin when metformin and a sulfonylurea no longer control their blood glucose. Clinical studies have suggested that the addition of a thiazolidinedione to the combination of metformin and a sulfonylurea decreases HbA1c levels by 0.6–1.8% over 6–36 months. In one placebo-controlled study of patients already receiving a sulfonylurea and metformin the addition of rosiglitazone resulted in a greater reduction in HbA1c levels (–0.9 v. +0.1%) and a larger proportion of patients achieving a HbA1c < 7% (42 v. 14%) after 24 weeks.[5]

The possible benefits of using a thiazolidinedione to delay starting insulin are less clear. One study randomised patients with secondary failure receiving both metformin and insulin secretagogues to the addition of pioglitazone or bedtime NPH insulin. After 16 weeks HbA1c levels were lowered to a similar degree with pioglitazone (–1.9%) or insulin (–1.5%) but hypoglycaemia was less common in patients treated with pioglitazone.[6]

Combined therapy with insulin

Thiazolidinediones have been used in combination with insulin. They lower HbA1c concentrations by 0.6–1.2% compared with placebo plus insulin. At present the PBS only lists the combination of pioglitazone and insulin. The combination of insulin, metformin (to improve hepatic insulin sensitivity) and a thiazolidinedione (to improve peripheral insulin sensitivity) has also been suggested as a useful approach to improve glucose metabolism in type 2 diabetes.

Non-hypoglycaemic effects and emerging indications

The established glycaemic, 'non-hypoglycaemic' and emerging indications for the use of thiazolidinediones are summarised in Table 2. Many of these emerging indications will require extensive research before they can be accepted into practice.

How to prescribe the thiazolidinediones

At present the available preparations are:

- pioglitazone 15, 30 and 45 mg tablets (daily dose)
- rosiglitazone 4 and 8 mg tablets (daily or twice-daily dose).

An authority prescription is required if the drugs are prescribed under the PBS. The PBS indications are restricted.

Approved indications under the PBS

Pioglitazone or rosiglitazone can be initiated as dual therapy with either metformin or a sulfonylurea. There must be a contraindication to or intolerance of therapy with metformin plus sulfonylureas and the patient's blood glucose concentrations must have been inadequately controlled. (Inadequate control is defined as HbA1c > 7%, despite diet, exercise and maximal-tolerated doses of metformin or sulfonylureas.)

Pioglitazone can also be initiated in combination with insulin, in patients with type 2 diabetes whose blood glucose concentrations are inadequately controlled by insulin alone. Inadequate control is defined as HbA1c > 7%, despite concomitant use of insulin and oral anti-diabetic drugs.

The initial application for an authority prescription requires the HbA1c concentration, the date of measurement and the reason for the contraindication or intolerance to either metformin or sulfonylureas. For repeat prescriptions the HbA1c should not have deteriorated since starting treatment and it should be under 8.5% on at least two occasions within 10 months of starting treatment. Pathology reports, from accredited laboratories, must be available with patients' records for audit by the Health Insurance Commission.

Table 2

Potential scope for thiazolidinedione use

Indication	Rationale
Prevention of type 2 diabetes	Thiazolidinediones improve insulin sensitivity and may preserve β-cell function. Trials are in progress to assess the effectiveness of thiazolidinediones in preventing the onset of type 2 diabetes.
Metabolic syndrome/insulin resistant states	A decrease in insulin resistance ameliorates the metabolic syndrome and its associations such as dyslipidaemia (see below), hypertension and microalbuminuria.
Dyslipidaemia	Thiazolidinediones raise concentrations of high density lipoprotein, with pioglitazone having the greatest effects. Pioglitazone also reduces triglycerides. Rosiglitazone raises low density lipoprotein (LDL) concentrations, but this is associated with a shift from small dense to large buoyant LDL particles that are thought to be less atherogenic. Whether this effect negates the increased cardiovascular risk associated with a raised LDL is unknown. Pioglitazone does not significantly increase LDL concentrations.
Cardiovascular protection	PPARγ receptors are present in vascular tissues. Thiazolidinediones may have protective effects on small and large blood vessels beyond those expected from glucose-lowering effects alone. Long-term studies are currently evaluating this possibility.
Polycystic ovary syndrome	Thiazolidinediones induce ovulation, and decrease insulin and androgen concentrations.
Non-alcoholic steatohepatitis	Improvements in liver function tests and liver biopsy findings have been reported.
Lipodystrophy (HIV and non-HIV related)	Thiazolidinediones alter fat distribution in non-HIV lipodystrophy. Although there is some evidence supporting the use of thiazolidinediones in HIV patients with lipodystrophy related to highly active antiretroviral use, this approach has not been supported by a recent randomised, double-blind clinical trial.
Effects on tumour growth	Thiazolidinediones have been shown to have both inhibitory and stimulatory effects in a variety of experimental models of tumour growth. As yet there have been no clinical studies.

Practice tips for prescribing the thiazolidinediones

- The maximal hypoglycaemic effects of thiazolidinediones may not be seen for up to three months; dose changes prior to this time are not recommended.
- Be wary of delayed onset hypoglycaemia.
- Thiazolidinediones are contraindicated if the patient's alanine aminotransferase concentrations are more than 2.5 times the upper limit of normal. The product information recommends that liver function is checked when starting treatment, every second month for the first year and then periodically thereafter.
- Thiazolidinediones should not be taken by women who are pregnant or breastfeeding. Women with polycystic ovary syndrome should be warned that thiazolidinediones may induce ovulation. They may need contraception.
- Not all patients will respond to thiazolidinedione therapy with a decrease in HbA1c.
- Guidelines for starting a thiazolidinedione and stopping metformin or a sulfonylurea have been prepared by the Australian Diabetes Society.

Conclusion

Deciding when a thiazolidinedione is appropriate requires consideration of their advantages and disadvantages. Potentially, the thiazolidinediones could be useful in the treatment of type 2 diabetes as they act to improve insulin sensitivity. However, the clinical evidence supporting their use is still very limited.[7] There is no current evidence to suggest that the glucose-lowering actions of thiazolidinediones are greater than those of other oral hypoglycaemic drugs. Thiazolidinediones might be shown to preserve β-cell function, alleviate many of the components of the metabolic syndrome/insulin resistance states, and offer cardiovascular protection. Both beneficial and adverse effects remain to be tested in large, long-term prospective clinical studies. Under current PBS criteria the main use of thiazolidinediones in Australia will most likely be in patients already taking a sulfonylurea who have an intolerance of or contraindication to metformin.

References

1. Nathan DM. Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. N Engl J Med 2002;347:1342-9.
2. Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes. Diabetes Care 2003;26:2983-9.
3. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003;108:2941-8, Diabetes Care 2004;27:256-63.
4. Boucher M, McAuley L, Brown A, Keely E, Skidmore B. Comparative clinical and budget evaluations of rosiglitazone and pioglitazone with other anti-diabetic agents. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2003. Technology overview no. 9.
5. Dailey GE 3rd, Noor MA, Park JS, Bruce S, Fiedorek FT. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med 2004;116:223-9.
6. Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am J Med 2004;116:230-5.
7. Gale EA. Lessons from the glitazones: a story of drug development. Lancet 2001;357:1870-5.

Both Dr MacIsaac and Professor Jerums have received speakers' fees and travel support from Eli Lilly and GlaxoSmithKline. Professor Jerums has also served on the advisory board for GlaxoSmithKline.

Self-test questions

The following statements are either true or false (answers on page 79)

7. The combination of insulin and a thiazolidinedione may precipitate heart failure.
8. The maximum fall in blood glucose concentrations occurs approximately one week after starting a thiazolidinedione.

More information about the listing of pioglitazone and rosiglitazone in the Schedule of Pharmaceutical Benefits is available on the National Prescribing Service RADAR web site at

http://www.npsradar.org.au/articles/pioglitazone.php
http://www.npsradar.org.au/articles/rosiglitazone.php

Taking care of thyroxine

Gregory W. Roberts, Clinical Pharmacist, Repatriation General Hospital, Daw Park, South Australia

Summary

Some of the pharmaceutical properties of thyroxine have important implications for the quality use of medicines. The stability of thyroxine tablets is limited and they may reach the expiry date before the bottle is finished. Administration should preferably be on an empty stomach and be consistent with respect to food and other drugs. The long half-life of thyroxine enables longer dosing intervals of up to a week if required. The two Australian brands of thyroxine are identical and patients can swap brands safely, but this should not be assumed for overseas brands.

Key words: hypothyroidism, hyperthyroidism, pharmacokinetics.

(Aust Prescr 2004;27:75–6)

Introduction

Thyroxine tablets are important in managing hypothyroidism, but treatment may be sub-optimal if they are used incorrectly. The tablets have pharmaceutical properties which can impair the patient's management. Discussing the correct use and storage of the tablets is an important part of prescribing thyroxine.

Availability

Synthetic preparations of thyroxine contain the *laevo* isomer of thyroxine, usually as the sodium salt. There are two brands of thyroxine available in Australia, each as 50 microgram, 100 microgram and 200 microgram tablets (pack size 200) with five repeats on the Pharmaceutical Benefits Scheme. Parenteral preparations of thyroid hormone have little use in Australia, outside of specialist centres.

The two Australian brands are marketed by Sigma and one of its subsidiaries. They are identical products so patients can swap them safely, but this assumption should **not** be extended to overseas brands.

Stability

Thyroxine is stable in dry air, but unstable in the presence of light, heat and humidity. In some cases overseas, thyroxine tablets have been unstable even at room temperature, and storage temperatures of 8°C to 15°C were required to maintain potency. In the USA, the Food and Drug Administration has determined that stability and potency problems with oral thyroxine preparations could potentially have adverse effects on health. It is therefore very important that thyroxine tablets should be kept in their original container and stored out of sunlight in a cool dry place.[1]

The expiry date for Australian manufactured thyroxine tablets is one year from the date of manufacture. There are 200 tablets in a bottle, so it is possible that patients on half tablet doses will not finish the bottle before the stock expires. The expiry date should be emphasised to the patient to ensure they do not continue taking a thyroxine preparation that may be waning in potency. However, stock with a shelf-life of 18 months will soon be available. This formulation will require refrigeration at all times.

Absorption

Thyroxine is variably absorbed from the gut following oral administration. It has a bioavailability of 40–80%. Absorption may decrease with age.[1,2]

The extent of thyroxine absorption is increased in the fasting state and is influenced by the content of the gastrointestinal tract. Some substances bind the thyroxine, making it unavailable for diffusion across the gut wall. Concurrent administration with iron salts, antacids, calcium carbonate (including milk), sucralfate, cholestyramine and soy-based formulas may therefore decrease absorption of thyroxine.

Administration

Patients should be instructed to take thyroxine 30–60 minutes before breakfast in order to maximise absorption. If this is too difficult or threatens compliance, the patient may try taking the thyroxine last thing at night on an empty stomach. Patients who still decide to take their tablets with, rather than before, breakfast need to do this consistently, to avoid fluctuating thyroxine concentrations. Depending on the fibre and milk content of the meal, taking thyroxine with food may require a larger dose to maintain euthyroidism, because of the decreased bioavailability.

While most patients take a daily dose, the long half-life of thyroxine lends itself to longer dosing intervals, such as alternate daily dosing. Once-weekly dosing is also possible although a slightly larger dose than seven times the normal daily dose may be required. This regimen may be suitable for poorly compliant patients who require supervised dosing.[3]

For patients, particularly children, who cannot swallow tablets, the tablets may be crushed in 10–20 mL of water, breast milk or non-soybean formula. The resulting mixture should be used immediately and any remainder discarded.[2] Breast milk contains

only 20–30% of the calcium concentration of cows milk, making the likelihood of decreased thyroxine bioavailability less likely. Nonetheless, if breast milk is used to deliver the thyroxine, it should be used consistently, in order to minimise any variation in absorption.

Onset and duration of action

The half-life of thyroxine in euthyroidism is 6–7 days. This is reduced to 3–4 days in hyperthyroidism and prolonged to 9–10 days in hypothyroidism. Thyroxine has a full therapeutic effect 3–4 weeks after starting treatment and will continue to have a therapeutic action for 1–3 weeks after treatment stops. In view of the long half-life, dose changes should only be made every 3–4 weeks. Despite undergoing both hepatic and renal clearance, there is no evidence that dose adjustment is required for patients with liver or kidney disease.[1,2]

Monitoring

The dosage is adjusted according to thyroxine and thyroid stimulating hormone plasma concentrations, which should always be interpreted in conjunction with each other and the patient's condition.[4] Monitoring is suggested at six-weekly intervals when starting therapy until the patient has stabilised, then six monthly thereafter, or earlier if symptoms suggestive of hyper- or hypothyroidism occur.

Drug interactions

Most drug interactions are seen during shifts to and from the euthyroid state and rarely have any clinical significance during periods of thyroid stability. The hyperthyroid state increases clearance of some hepatically cleared drugs, notably propranolol, metoprolol and theophylline. Antacids, iron salts, calcium carbonate (milk), sucralfate, cholestyramine and soy-based formulas reduce the absorption of thyroxine.

Conclusion

There are significant stability, absorption and drug interaction issues surrounding the use of thyroxine. It is essential that prescribers and pharmacists convey this information to patients in order that therapeutic efficacy may be maximised.

References

1. AHFS drug handbook. 2nd ed. Bethesda (MD): American Society of Health-System Pharmacists, Lippincott Williams & Wilkins; 2003.
2. Thomas J, editor. Australian Prescription Products Guide 2003. 32nd ed. Hawthorn: Australian Pharmaceutical Publishing Company Limited; 2003.
3. Grebe SK, Cooke RR, Ford HC, Fagerstrom JN, Cordwell DP, Lever NA, et al. Treatment of hypothyroidism with once weekly thyroxine. J Clin Endocrinol Metab 1997;82:870-5.
4. Australian Medicines Handbook 2004. Adelaide: Australian Medicines Handbook Pty Ltd; 2004.

Further reading

Toft AD. Clinical practice. Subclinical hyperthyroidism. N Engl J Med 2001;345:512-6.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

9. The dose of thyroxine should be decreased in patients with renal failure.
10. Food increases the absorption of thyroxine tablets.

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 Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Aprepitant

Emend (Merck Sharp and Dohme)

80 mg and 125 mg capsules

Approved indication: emetogenic cancer chemotherapy

Australian Medicines Handbook section 12.3

Many anticancer drugs induce nausea and vomiting. Cisplatin is particularly toxic and induces vomiting which can last for days. Although anti-emetic regimens can control some of the symptoms, possibly half the patients treated with highly emetogenic chemotherapy continue to suffer nausea and vomiting.

To address the problem, researchers have looked at the role of substance P in vomiting. This peptide is found in the brain and the gut and its actions are mediated through the neurokinin-1 receptor. Blocking this receptor may prevent vomiting.

Aprepitant is a selective antagonist of the neurokinin-1 receptor which can cross the blood-brain barrier. It has no affinity for serotonin ($5HT_3$) or dopamine (D_2) receptors.

Patients take aprepitant orally once a day for three days, starting one hour before chemotherapy. The drug is slowly absorbed and extensively metabolised. As it has non-linear pharmacokinetics increasing the dose reduces bioavailability and clearance.

The metabolism involves cytochrome P450 3A4 so there is a potential for interaction with other drugs, such as midazolam, metabolised by this system. Aprepitant also induces the metabolism of warfarin. The half-life of aprepitant is 9–13 hours.

Aprepitant was tested in a variety of combinations with dexamethasone, granisetron ($5HT_3$ antagonist) and a placebo in 351 patients having cisplatin for the first time. In the first 24 hours after treatment, 80% of the patients given granisetron, dexamethasone and aprepitant had no vomiting compared with 57% of those treated with granisetron and dexamethasone. Delayed emesis was prevented in 63% of the patients taking the three drugs, but in only 29% of those taking granisetron and dexamethasone.[1]

In this trial there was no extra benefit in giving aprepitant for five days. Another trial therefore compared a three-day regimen with a standard regimen of ondansetron and dexamethasone. The 530 patients had not previously been treated with cisplatin. There was no acute vomiting in 89% of the patients given aprepitant, ondansetron and dexamethasone compared with 78% of those given the standard regimen. Delayed emesis did not occur in 75% of the patients taking aprepitant and 56% of those taking the standard regimen.[2] Another randomised placebo-controlled trial produced similar results.[3]

As patients with cancer usually require several doses of chemotherapy, another trial has studied two regimens of aprepitant given during six cycles of cisplatin. All 202 patients received a standard regimen of ondansetron and dexamethasone. The prevention of emesis declined from 49% to 34% after six cycles in patients treated with the standard regimen. In patients who also took aprepitant, 64% had no vomiting after the first cycle and 59% had no vomiting after the sixth cycle.[4]

Assessing adverse events in patients who are given multiple drugs for their cancers can be difficult. Adverse events associated with regimens containing aprepitant include hiccups, asthenia, headache and altered liver function.

Although the efficacy of aprepitant has been proven, questions remain about its role in practice. As treatment guidelines often include metoclopramide for the prevention of delayed emesis, aprepitant should be compared with such regimens. There also needs to be more study of the effectiveness of aprepitant in subsequent cycles of chemotherapy. Although the results of the trial[4] look promising, few patients completed six cycles of chemotherapy. At present aprepitant can only be used with highly emetogenic chemotherapy, including high-dose cisplatin.

References †

1. Campos D, Pereira JR, Reinhardt RR, Carracedo C, Poli S, Vogel C, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. J Clin Oncol 2001;19:1759-67.
2. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – the Aprepitant Protocol 052 Study Group. J Clin Oncol 2003;21:4112-9.
3. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Ma GJ, Eldridge K, Hipple A, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer 2003;97:3090-8.
4. de Wit R, Herrstedt J, Rapoport B, Carides AD, Carides G, Elmer M, et al. Addition of the oral NK_1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003;21:4105-11.

Iloprost

Ventavis (Schering)

Ampoules containing 20 microgram (10 microgram/mL) nebuliser solution

Approved indication: pulmonary hypertension

Australian Medicines Handbook section 6.7.3

Increased pressure in the pulmonary artery may have no obvious cause or it may be secondary to conditions such as thromboembolism and connective tissue diseases.[1] It leads to signs of right-sided heart failure, such as peripheral oedema and liver enlargement.

Some secondary causes can be treated. For example, pulmonary artery hypertension due to chronic thromboembolism may respond to pulmonary thromboendarterectomy. Some patients with advanced disease may live long enough to receive a heart-lung transplant.

Patients with pulmonary hypertension may have an imbalance of prostacyclin and thromboxane A_2. Giving an analogue of prostacyclin may therefore induce vasodilatation and reduce pressure in the pulmonary artery. Epoprostenol was approved for use in primary pulmonary hypertension in 2002, but it has to be given by continuous intravenous infusion. Treprostinil was approved in 2003, but requires continuous subcutaneous infusion. Iloprost is also an analogue of prostacyclin, but it can be given by inhalation.

Patients inhale a nebulised solution over 5–10 minutes. The serum concentration of iloprost peaks at the end of the inhalation but declines rapidly. Iloprost is extensively metabolised and none can be detected an hour after the inhalation. Some patients will need to take a dose nine times a day. Most of the metabolites are excreted in the urine, so clearance can be reduced by renal and hepatic dysfunction.

A randomised-controlled trial compared iloprost with an inhaled placebo in 203 patients with primary or secondary pulmonary hypertension. After 12 weeks, function had improved in 16.8% of the patients given iloprost, but only in 4.9% of those given a placebo.[2]

Another study enrolled 31 patients with primary pulmonary hypertension and followed them for a year. The mean

pulmonary artery pressure was reduced in the 24 people who completed the study. This was associated with an increased exercise capacity.[3]

While dyspnoea improves with iloprost, coughing is common in the first weeks of treatment. Patients may also complain of flushing and pain in the jaw. Other common adverse effects are hypotension, syncope, trismus and headache.

Although iloprost is significantly better than placebo the absolute benefits are limited. In the placebo-controlled study patients given iloprost for 12 weeks were able to walk an extra 36.4 metres in six minutes.[2] Few of the patients with secondary pulmonary hypertension gained much benefit. Iloprost has been approved for secondary pulmonary hypertension for a strictly limited range of conditions.

Inhaled iloprost is likely to be cheaper than intravenous epoprostenol, but epoprostenol is proven to increase survival in patients with primary pulmonary hypertension. In contrast to the other prostacyclin analogues, iloprost is given intermittently. It is uncertain whether there could be a rebound in the pulmonary artery pressure between inhalations.

In addition to the prostacyclin analogues bosentan, an oral endothelin receptor antagonist, is also available to treat primary pulmonary hypertension. Comparative studies are therefore needed to determine the best medical therapy.

References

1. Keogh AM, McNeil KD, Williams T, Gabbay E, Cleland LG. Pulmonary arterial hypertension: a new era in management. Med J Aust 2003;178:564-7.
2. Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347:322-9.
3. Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med 2000;342:1866-70.

Methyl-5-aminolevulinate

Metvix (Galderma)

2 g tubes of cream containing 160 mg/g

Approved indications: actinic keratoses, basal cell carcinoma

Australian Medicines Handbook section 14.3

Squamous cell carcinomas can develop from actinic keratoses. While some keratoses will resolve with reduced exposure to sunlight others need to be removed. As an alternative to surgical treatments, severe cases can be treated with topical fluorouracil. Methyl-5-aminolevulinate, which is a porphyrin precursor, is another antineoplastic drug that can be applied directly to the lesions.

After applying methyl-5-aminolevulinate, the lesion is covered with an occlusive dressing for three hours. This results in the accumulation of the porphyrins which are produced by the enzymatic conversion of methyl-5-aminolevulinate. The lesion is then exposed to a dose of red light. This light activates the intracellular porphyrins causing damage to the cells. The treatment is repeated one week after the first application. If there is no response after three months the patient can be re-treated once.

In an Australian study there was a complete response in 71 of 88 patients with solar keratoses. A placebo cream resulted in only three of 23 patients responding. The complete response rate of 81% was greater than the 60% who responded to one treatment of cryotherapy. A European study also compared the two treatments, but found that the response rate to cryotherapy was higher (75%) than the response to methyl-5-aminolevulinate (69%).[1]

Methyl-5-aminolevulinate can also be used to treat basal cell carcinoma. Although a few more patients will respond to photodynamic therapy than cryotherapy (95% v 91%), the response rate is less than that of surgical excision (90% v 98%). Recurrences are also less likely after surgical excision, but photodynamic therapy may give a better cosmetic outcome. Methyl-5-aminolevulinate can therefore be considered for superficial or nodular basal cell carcinomas where surgery is inappropriate.

As methyl-5-aminolevulinate is a photosensitiser it can cause phototoxic reactions. Patients should not expose the treated areas and surrounding skin to sunlight for two days after treatment. Burning, pain, redness and oedema are very common adverse effects. Some patients develop blisters or skin ulcers. In the European study more of the patients had a reaction to methyl-5-aminolevulinate than to cryotherapy (43% v 26%).[1]

Methyl-5-aminolevulinate works best on keratoses which are not hyperkeratotic. If treatment is successful it gives a good cosmetic result. It can therefore be considered for thin lesions on the face or scalp when other treatments are unsuitable.

Reference

1. Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol 2002;47:258-62.

NEW FORMULATIONS

Amisulpride

Solian solution (Sanofi-Synthelabo)

100 mg/mL oral solution

Metoprolol succinate

Toprol-XL (AstraZeneca)

23.75 mg, 47.5 mg, 95 mg and 190 mg controlled-release tablets

Approved indication: chronic heart failure

Australian Medicines Handbook section 6.4.3

Beta blockers used to be contraindicated in heart failure, but they can benefit some patients with chronic stable heart failure.[1]

A placebo-controlled study of 3991 patients who were already on optimum therapy, such as a diuretic and an ACE inhibitor, found that metoprolol significantly reduced deaths. After a year the mortality rate was 7.2% in the metoprolol group and 11% in the placebo group.[2]

The preparation used in the clinical trial was an extended-release formulation. This contained metoprolol succinate as opposed to metoprolol tartrate which is used in the treatment of angina and hypertension.

The two salts of metoprolol have been compared in a haemodynamic study. This found that both salts had similar effects.[3] The extended-release formulation is given once a day. Its peak plasma concentrations are only 25% or 50% of those of the conventional formulation, but they produce comparable beta blockade over 24 hours.

When the extended-release tablets are prescribed for heart failure, the dose must be slowly increased over several weeks. If the heart failure gets worse during this titration metoprolol succinate may need to be discontinued.

References

1. Fletcher P. Beta blockers in heart failure. Aust Prescr 2000;23:120-3.
2. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.
3. Kukin ML, Mannino MM, Freudenberger RS, Kalman J, Buchholz-Varley C, Ocampo O. Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. J Am Coll Cardiol 2000;35:45-50.

Further reading

http://www.npsradar.org.au/articles/metoprolol.php

† At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

Answers to self-test questions

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

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