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CONTENTS

EDITORIAL

Retail genetics

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Keywords
advertising, genetic testing, pharmacogenomics

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General practitioners are increasingly encountering patients who have paid for a genetic profile.[1,2] These direct-to-consumer tests are promoted through community pharmacies or other retailers, by mail order or via the internet. They usually involve the collection of cellular material from cheek swabs or saliva which is sent to a laboratory that analyses the DNA using chip array-based genotyping.[3] These differ from the clinical genetic services that GPs can refer patients to.

Direct-to-consumer tests usually have no involvement of a medical practitioner when they are ordered and limited or no counselling is provided. Companies promoting direct-to-consumer genetic tests usually claim they are for consumer information rather than medical decision making. However, the breadth of the genetic profiles produced, particularly by predictive or pre-symptomatic genetic tests, may impact on family members, potential employment and life insurance.

Preventive care is fundamentally about risk assessment and management of a condition with a patient's family history playing a role. This is one area where, with the appropriate training of health professionals, genetic profiles have the possibility to inform care. Despite this, direct-to-consumer genetic test reports are difficult to interpret. In 2012 only 7% of Australian genetic specialists reported they would be confident to interpret and explain the results of these tests.[4]

Some companies specialise in pharmacogenomic tests that suggest how an individual's genetic make-up may affect their response to certain drugs. One company pays pharmacists to collect the test and interpret the result for the consumer. The results are also sent to the patient's GP.[3] Pharmacogenomic tests can sometimes be a useful alternative to selecting drugs by trial and error, especially if a patient has experienced a poor response to treatment or unexpected adverse effects. However, a 'normal' pharmacogenomic test does not mean the patient is not at risk of drug-related adverse effects, or of not responding to a drug. Current tests only capture known variants of known genes. In addition, even if the test shows gene variants that impact on a certain drug's metabolism, this is only one of many factors that influence how patients respond to drug therapy. Other factors include age, weight, drug interactions, allergies, renal and liver function, and psychosocial characteristics such as impaired cognition and health literacy.

Some GPs have expressed disquiet at receiving test results they have not ordered and the interpretation may be difficult. While knowledge in this area is increasing, in many specific clinical situations more work is required to ensure that test results will be meaningfully translated into clinical practice in order to achieve best outcomes for the patient.[5]

The Australian Competition and Consumer Commission (ACCC) has been concerned that, in one case, some statements about genetic testing (in pharmacy catalogues, television infomercials, in-store brochures and other promotional materials) 'risked conveying a false or misleading impression regarding the usefulness of the test and the consumers for whom testing may be appropriate'. Consequently, following ACCC intervention, the promotional materials containing statements of concern were withdrawn.[6]

Some companies risk over-enthusiastic promotion. For example, testing for the AMY1 gene is claimed to reveal how well the body can metabolise starch carbohydrates. This test is said to assist with a range of weight management and other health issues. One company recommends its own preferred practitioners who offer 'nutrigenomics' advice, based on the test result, for a variety of health conditions.[7]

There are also overseas companies that promote their tests in Australia via the internet. One offers genetic tests for 31 disease conditions, 53 carrier status conditions, 12 drug response genes, 6 wellness tests, 11 traits and 11 addictions.[8] These claims appear to go well beyond the evidence base underlying the tests and do not come under the jurisdiction of Australian regulators.

Direct-to-consumer genetic profiling tests provided by Australian companies or laboratories for self-testing are classified as Class 3 in vitro diagnostic medical devices by the Therapeutic Goods Administration (TGA). Until 2010, the level of regulation in Australia was very limited. A new regulatory framework began on 1 July 2010 to ensure that all such tests undergo a level of regulatory scrutiny commensurate with their risks. Commercial medical device manufacturers must now seek a conformity assessment certificate from the TGA if they want to supply such products in Australia.

From July 2017 local laboratories who develop medical devices 'in-house' must maintain their accreditation by the National Association of Testing

Authorities, Australia (NATA). Their tests must also meet National Pathology Accreditation Advisory Council performance standards.

It remains unclear what the potential impact of genetic profiling may be on purchasing various types of insurance, particularly life insurance. While private health insurance companies do not require consumers to undertake tests to assess the risk of disease, and premiums are not affected by the genetic test results, you are required to disclose information that may impact your insurability. Underwritten life insurance products, including cover for life, trauma, disability and income protection which may be required for business and bank loans, could be impacted by a genetic test result.

In conclusion, health professionals and consumers need to be aware that genetic tests developed in-house will not undergo regulatory scrutiny by the TGA until July 2017. In addition, promotional claims may exceed the evidence underlying the test. Furthermore, their cost is not covered by Medicare or private health insurance rebates, except for some tests, such as those that can guide cancer treatment. Health professionals should advise their patients not to purchase these tests from overseas. Patients should also discuss the usefulness of locally promoted tests with their doctor before paying for a test.

There needs to be ongoing education of all health professionals about the appropriateness and changing role of these tests as more knowledge becomes available. The education should be in keeping with useful information provided by the National Health and Medical Research Council for both consumers and medical practitioners.[9] This ongoing education should be independent of the companies promoting the test. <

Conflict of interest: none declared

REFERENCES

1. Schneider KA, Schmidtk J. Patient compliance based on genetic medicine: a literature review. J Community Genet 2014;1:31-48. http://dx.doi.org/ 10.1007/s12687-013-0160-2
2. Blashki G, Metcalfe S, Emery J. Genetics in general practice. Aust Fam Physician 2014;43:428-31.
3. MyDNA [Internet]. Melbourne: My DNA Life Australia Pty Ltd; 2016. https://www.mydna.life [cited 2017 May 1]
4. Brett GR, Metcalfe SA, Amor DJ, Halliday J. An exploration of genetic health professionals' experience with direct-to-consumer genetic testing in their clinical practice. Eur J Hum Genet 2012;20:825–30. http://dx.doi.org/10.1038/ejhg.2012.13
5. Bousman CA, Hopwood M. Commerical pharmacogenetics-based decision-support tools in psychiatry. Lancet Psychiatry 2016;3:585-90. http://dx.doi.org/10.1016/S2215-0366(16)00017-1
6. Australian Competition and Consumer Commission. Chemmart agrees to improve its promotion of 'myDNA' tests [media release]. 2016 Sept 12. http://www.accc.gov.au/media-release/chemmart-agrees-to-improve-its-promotion-of-%E2%80%9Cmydna%E2%80%9D-tests [cited 2017 May 1]
7. Fitgenes Personalised Health. Carb choice and your AMY1 CNV [Internet]. Melbourne: Fitgenes; 2017. www.fitgenes.com/health-and-wellbeing/Fitgenes-Profile-Reports/carb-choice-amy1 [cited 2017 May 1]
8. VIAMEDEX Genetic and Drug Testing Laboratory. Genetic predisposition test [Internet]. VIAMEDEX Genetic Laboratories; 2016. http://geneticaustralia.com/genetic-predisposition.php [cited 2017 May 1]
9. National Health and Medical Research Council. Direct-to-consumer genetic testing: a statement from the National Health and Medical Research Council (NHMRC). Canberra: Commonwealth of Australia; 2014. www.nhmrc.gov.au/guidelines-publications/g9

FURTHER READING

Somogyi AA, Phillips E. Genomic testing as a tool to optimise drug therapy. Aust Prescr 2017;40:101-4. http://dx.doi.org/10.18773/austprescr.2017.027

LETTERS

Letters to the Editor

Pharmacokinetics of apixaban

Aust Prescr 2017;40:88
http://dx.doi.org/10.18773/austprescr.2017.033

I have recently been updating information on the new oral anticoagulants for NPS MedicineWise. I used your article[1] as a starting point to see what references have been published since 2013.

In reviewing the pharmacokinetics of apixaban, I got confused and so did some further research. I found a Letter to the Editor on the topic.[2] It essentially explains that the commonly quoted number of 50% for renal clearance is flawed due to a calculation error between the primary and secondary source.

Penny Beirne
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NPS MedicineWise

REFERENCES

1. Chin PKL, Doogue MP. Long-term prescribing of new oral anticoagulants. Aust Prescr 2016;9:200-4. http://dx.doi.org/10.18773/austprescr.2016.068
2. Frost C, Boyd RA. The contribution of apixaban renal clearance to total clearance. J Thromb Thrombolysis 2015;40:521-2. http://dx.doi.org/10.1007/s11239-015-1220-8

Paul Chin and Matthew Doogue, the authors of the article, comment:

Penny Beirne highlights the inconsistent reporting in the literature of the fraction of unchanged apixaban excreted in urine. This has also recently been noted by others.[1] The key article that informed our estimates of apixaban oral bioavailability was a mass balance study.[2] It reported that around 25% of an orally administered dose was excreted unchanged in urine. When corrected for an oral bioavailability of 50%, this translates to a fraction of 0.5 excreted unchanged in urine. However, this estimate is made in the absence of data on intravenously administered apixaban.

Since reviewing the literature following this letter, we found another apixaban pharmacokinetic study.[3] It reported that the fraction of apixaban excreted unchanged in urine following intravenous administration was 0.34. We thus concur with Penny Beirne and would like to change the apixaban value for 'excretion unchanged in urine' in the Table of our article to 34%.

REFERENCES

1. Hellfritzsch M, Damkier P, Pottegard A, Gronlykke T, Grove EL. Inconsistencies in reporting of renal elimination among NOACs: the case of apixaban. Pharmacoepidemiol Drug Saf 2016;25:346-8. http://dx.doi.org/10.1002/pds.3916
2. Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos 2009;37:74-81. http://dx.doi.org/10.1124/dmd.108.023143
3. Vakkalagadda B, Frost C, Byon W, Boyd RA, Wang J, Zhang D, et al. Effect of rifampin on the pharmacokinetics of apixaban, an oral direct inhibitor of factor Xa. Am J Cardiovasc Drugs 2016;16:119-27. http://dx.doi.org/10.1007/s40256-015-0157-9

Editorial note:

The original article on long-term prescribing of new oral anticoagulants has been corrected based on this letter from the authors.

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

Compounded medicines

Aust Prescr 2017;40:89
http://dx.doi.org/10.18773/austprescr.2017.034

I have just read the excellent article regarding extemporaneously compounded medicines.[1] I found it very informative and useful but there were several points that were not fully explained or were omitted.

To meet the Therapeutic Goods Administration (TGA) exemption, compounding must be for an individual patient (only stated in the conclusion) and cannot be in 'bulk'.

Compounded medicines cannot be supplied by wholesale, for example from one pharmacy to another.

In NSW, an authority is required by a prescriber from the NSW Ministry of Health for compounded Schedule 8 drugs. This authority number must be written on the prescription form.

Several TGA-licensed companies prepare compounded medicines in bulk and hold a wholesale licence to provide those medicines to, for example, hospitals under contract.

The Pharmacy Board of Australia guidelines and the TGA specify that compounding should *not* occur if a product on the Australian Register of Therapeutic Goods is available. This includes, for example, the addition of ingredients to products and the variation of the strength of a product, where such changes have no significance with regard to the indications or efficacy of the final product. Some compounding pharmacists seem to be able to convince prescribers that this practice is legitimate.

Alex Gavrilovic
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REFERENCE

1. Falconer JR, Steadman KJ. Extemporaneously compounded medicines. Aust Prescr 2017;40:5-8. http://dx.doi.org/10.18773/austprescr.2017.001

LETTERS

Safety concerns with the direct-acting antivirals for hepatitis C

Aust Prescr 2017;40:90
http://dx.doi.org/10.18773/austprescr.2017.036

Simone Strasser's summary of hepatitis C treatment in general practice deserves comment.[1]

Although the rate of sustained virologic response to direct-acting antivirals is impressive, this is only a surrogate. Interferon-based regimens were proven to have efficacy on the rate of progression to cirrhosis and the incidence of hepatocellular carcinoma. Expectation with direct-acting antivirals cannot replace the results of either long-term randomisation on clinically relevant benefits and harms or post-marketing surveillance programs. Indeed, safety concerns are beginning to come to light.[2] Moreover, an unusual occurrence of hepatocellular carcinoma among patients with direct-acting antiviral therapy has been reported.[3] The finding needs more basic data to be analysed but the fourfold increase in serum vascular endothelial growth factor during antiviral therapy is alarming.[4]

Simone Strasser rightly stressed the importance of treating comorbid factors such as alcohol use and obesity in patients with hepatitis C. However, she overlooked the case of smoking, which is an independent and dose-related cause of hepatocellular carcinoma. In a large European study of patients with hepatocellular carcinoma, the population-attributable fraction for tobacco use was 47.6%. This was more than twice the population-attributable fraction for hepatitis C (at 20.9%), which was the second most attributed risk factor.[5]

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REFERENCES

1. Strasser S. Managing hepatitis C in general practice. Aust Prescr 2017;40:64-9. http://dx.doi.org/10.18773/austprescr.2017.017
2. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another direct acting antiviral drug. 2015 Mar 24. www.fda.gov/Drugs/DrugSafety/ucm439484.htm [cited 2017 May 1]
3. Ravi S, Axley P, Jones D, Kodali S, Simpson H, Mcguire BM, et al. Unusually high rates of hepatocellular carcinoma after treatment with direct-acting antiviral therapy for hepatitis C related cirrhosis. Gastroenterology 2017;152:911-2. http://dx.doi.org/10.1053/j.gastro.2016.12.021
4. Villani R, Facciorusso A, Bellanti F, Tamborra R, Piscazzi A, Landriscina M, et al. DAAs rapidly reduce inflammation but increase serum VEGF level: a rationale for tumor risk during anti-HCV treatment. PLoS One 2016;11:e0167934. http://dx.doi.org/10.1371/journal.pone.0167934
5. Trichopolous D, Bamia C, Lagiou P, Fedirko V, Trepo E, Jenab M, et al. Hepatocellular carcinoma risk factors and disease burden in a European cohort: a nested case-control study. J Natl Cancer Inst 2011;103:1686-95. http://dx.doi.org/10.1093/jnci/djr395

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ARTICLE

Peptic ulcer disease and non-steroidal anti-inflammatory drugs

SUMMARY

Non-steroidal anti-inflammatory drugs including low-dose aspirin are some of the most commonly used medicines. They are associated with gastrointestinal mucosal injury.

Before prescribing, it is important to assess the patient's gastrointestinal risk factors such as age and history of peptic ulcers. Patients at high risk may require co-prescription to reduce the risk of peptic ulcers.

A daily dose of a proton pump inhibitor is the most effective method of reducing the risk of ulcers induced by non-steroidal anti-inflammatory drugs.

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Keywords
misoprostol, non-steroidal anti-inflammatory drugs (NSAIDs), peptic ulcers, proton pump inhibitors

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CPD FOR PHARMACISTS

This article has a continuing professional development activity for pharmacists available at http://learn.nps.org.au

Introduction

A peptic ulcer is a defect in the upper gastrointestinal mucosa that extends through the muscularis mucosa into deeper layers of the gut wall. There are two major risk factors for peptic ulcer disease – *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs including low-dose aspirin are some of the most commonly used drugs. They have good efficacy and a long history of clinical use, but can cause peptic ulcers which may have fatal complications.[1] Given widespread use of NSAIDs and aspirin, the associated gastrointestinal toxicities have substantial implications for the healthcare system.[2]

Mechanism of action

The therapeutic effects of NSAIDs are mediated by their inhibition of prostanoid biosynthesis.[3] Prostanoid derivatives arise from the conversion of arachidonic acid by cyclo-oxygenase (COX) isoenzymes following cell injury.

There are two distinct isoforms of COX. COX-1 is present in the majority of cells including endothelial cells, gastrointestinal epithelium and platelets, and functions continuously. In contrast COX-2 is present in only a few tissues and is induced by inflammation. NSAIDs exert their therapeutic anti-inflammatory and analgesic effects by inhibiting COX-2. The gastric and renal toxicities of the drugs are related to inhibition of the COX-1 isoform.[4,5] There is a spectrum of COX-1 and COX-2 inhibition across the class of NSAIDs.

Ulcers and NSAIDs

Peptic ulcer disease is a well-recognised complication of NSAID use. Inhibition of COX-1 in the gastrointestinal tract leads to a reduction of prostaglandin secretion and its cytoprotective effects in gastric mucosa. This therefore increases the susceptibility to mucosal injury.[6] Inhibition of COX-2 may also play a role in mucosal injury.

Risk factors

Gastrointestinal toxicity with NSAIDs, including low-dose aspirin, is highest in patients with risk factors. These include increased age (>65 years), past history of peptic ulcer disease, heart disease, and co-prescription of antiplatelets, corticosteroids and anticoagulants. In addition, using higher doses of NSAIDs leads to an increased risk of upper gastrointestinal complications.[7] Prolonged NSAID use and *H. pylori* infection are also associated with an increased risk of gastrointestinal toxicity.

In patients who are chronic users of NSAIDs and who have no risk factors, only 0.4% have serious adverse events. However, the risk is as high as 9% in patients with multiple risk factors.[8] Before prescribing for a patient with risk factors always consider if there are alternatives to NSAIDs.

Which NSAID to use?

All NSAIDs cause some degree of gastrointestinal toxicity. Large pooled data from placebo-controlled trials show that all evaluated NSAIDs including COX-2 inhibitors, diclofenac, ibuprofen and naproxen were associated with an increased risk of gastrointestinal injury.[9] However, this risk varies between the drugs. The relative risk of upper gastrointestinal complications for aceclofenac, celecoxib and ibuprofen is low (<2). Diclofenac, meloxicam and ketoprofen are intermediate (2–4) while naproxen, indomethacin and diflunisal have a higher relative risk (4–5). The highest pooled relative risk is associated with piroxicam (7.4) and ketorolac (11.5).[7]

Drugs with greater selectivity for COX-2 than COX-1 should have less gastrointestinal toxicity. Large pooled data showed that the predicted absolute annual risk of upper gastrointestinal complications was lower for COX-2 inhibitors than naproxen and ibuprofen.[7] However, COX-2 inhibitors are associated with an increased risk of cardiovascular events. There is little evidence of an increased risk of cardiovascular complications with use of a low dose of diclofenac. However, to avoid possible cardiovascular complications the use of NSAIDs should be at the lowest possible dose and for the shortest time.

Low-dose aspirin

Low-dose aspirin is widely prescribed to reduce cardiovascular and cerebrovascular thromboembolic events. Patients who use low-dose aspirin tend to be older and likely to use concurrent antiplatelet or anticoagulant drugs that would lead to an increased risk of gastrointestinal toxicity. It has been shown that the relative risk for gastrointestinal toxicity such as bleeding is as high as 4 in high-risk patients. Meta-analysis of randomised controlled trials of 57 000 patients taking low-dose aspirin revealed a relative risk of 2 for significant gastrointestinal adverse events such as bleeding.[10] In patients with a history of ulcer bleeding consideration needs to be given to secondary ulcer prevention with proton pump inhibitor therapy. Changing aspirin to other antiplatelet therapy is not recommended.

Strategies to reduce gastrointestinal toxicity

Caution is needed to minimise the known adverse effects. Before prescribing, the medical history needs to be reviewed in order to assess the risk of gastrointestinal toxicity. This includes asking about the use of over-the-counter aspirin and NSAIDs. Consideration needs to be given to the choice of NSAID and the duration of therapy. Patients need to be informed and be aware of potential serious adverse events.

Proton pump inhibitors

Proton pump inhibitors reduce the secretion of gastric acid by inhibiting H^+/K^+-ATPase. They are widely used to induce healing of gastric and duodenal ulcers. In a double-blind randomised trial, a standard dose of proton pump inhibitor therapy was efficacious in ulcer healing and preventing recurrence of gastroduodenal injury in patients taking NSAIDs.[11] Proton pump inhibitors are slightly better at preventing duodenal ulcers than gastric ulcers.[12]

A recent meta-analysis assessed current strategies for the prevention of gastrointestinal toxicity. It found that selective COX-2 inhibitors in combination with proton pump inhibitors were associated with the lowest absolute event probability for ulcer complications (0.07; 95% confidence interval 0.02–0.18).[13] This strategy may be the most effective way to reduce the risk of ulcer complications, followed by the use of a selective COX-2 inhibitor alone and a non-selective NSAID combined with a proton pump inhibitor. Importantly all three strategies were well tolerated by patients. Due to their acceptable adverse effect profile, proton pump inhibitors have assumed therapeutic dominance for minimising the gastrointestinal risks of NSAIDs.

H_2-receptor antagonists

H_2-receptor antagonists have an adverse effect profile that is comparable to proton pump inhibitor therapy. However, the pooled data analysis showed that a single daily dose does not protect against NSAID-related gastric ulcers, but double doses of H_2-receptor antagonist (at least ranitidine 300 mg twice daily) were effective in preventing gastric and duodenal ulcers when compared to placebo.[14]

Misoprostol

Misoprostol is an analogue of prostaglandin E_1. Its gastro-protective effect is achieved by inhibition of gastric acid and pepsin release and it improves the resistance of the gastric mucosa. This effect is largely dose dependent. A large pooled data analysis showed misoprostol was effective in preventing gastric (74%) and duodenal ulcers (53%) in comparison with placebo.[10] Unfortunately, the clinical usefulness of the misoprostol is limited largely by its gastrointestinal adverse effects such as cramping, abdominal pain and diarrhoea, making it a third-line drug option.

Helicobacter pylori and NSAIDs in peptic ulcer disease

Testing for *H. pylori* for ulcer prevention in asymptomatic patients needs to be assessed on a case-by-case basis and is not routinely recommended. However, testing and eradicating *H. pylori* is recommended in patients with a past history of peptic ulcer disease before starting low-dose aspirin or NSAIDs.[15]

Conclusion

Chronic use of NSAIDs including low-dose aspirin is associated with gastrointestinal mucosal injury. However, major adverse events are relatively infrequent. Patients with multiple risk factors such as a previous history of peptic ulcer disease, increasing age, co-prescription of corticosteroids and anticoagulants, and high-dose and long-term use of NSAIDs are at the highest risk of major gastrointestinal toxicity. In patients with multiple risk factors, physicians need

to assess these risks before prescribing NSAIDs and adopt risk-minimising strategies.

Simple measures such as using the lowest dose for short periods of time when possible will prevent some of the NSAID-related toxicity. Selective COX-2 inhibitors also will reduce gastrointestinal adverse events when compared to non-selective NSAIDs. Proton pump inhibitor therapy is efficacious and has an acceptable adverse effect profile in comparison with misoprostol.

Before prescribing an NSAID, prophylactic proton pump inhibitor therapy needs to be offered to patients with a past history of peptic ulcer disease and those on dual antiplatelet therapy or anticoagulant therapy. <

Conflict of interest: none declared

REFERENCES

1. Atchison JW, Herndon CM, Rusie E. NSAIDs for musculoskeletal pain management: current perspectives and novel strategies to improve safety. J Manag Care Pharm 2013;19(Suppl A):1-19. http://dx.doi.org/10.18553/jmcp.2013.19.s9.1
2. Smalley WE, Griffin MR, Fought RL, Ray WA. Excess costs from gastrointestinal disease associated with nonsteroidal anti-inflammatory drugs. J Gen Intern Med 1996;11:461-9. http://dx.doi.org/10.1007/BF02599040
3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011;31:986-1000. http://dx.doi.org/10.1161/ATVBAHA.110.207449
4. Dvornik DM. Tissue selective inhibition of prostaglandin biosynthesis by etodolac. J Rheumatol Suppl 1997;47:40-7.
5. Robinson DR. Regulation of prostaglandin synthesis by antiinflammatory drugs. J Rheumatol Suppl 1997;47:32-9.
6. Brune K, Patrignani P. New insights into the use of currently available non-steroidal anti-inflammatory drugs. J Pain Res 2015;8:105-18. http://dx.doi.org/10.2147/JPR.S75160
7. Castellsague J, Riera-Guardia N, Calingaert B, Varas-Lorenzo C, Fourrier-Reglat A, Nicotra F, et al. Individual NSAIDs and upper gastrointestinal complications. Drug Saf 2012;35:1127. http://dx.doi.org/10.1007/BF03261999
8. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769-79. http://dx.doi.org/10.1016/S0140-6736(13)60900-9
9. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241-9. http://dx.doi.org/10.7326/0003-4819-123-4-199508150-00001
10. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624-38. http://dx.doi.org/10.1016/j.amjmed.2005.10.039
11. Hawkey CJ, Karrasch JA, Szczepański L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. Omeprazole versus misoprostol for NSAID-induced ulcer management (OMNIUM) study group. N Engl J Med 1998;338:727-34. http://dx.doi.org/10.1056/NEJM199803123381105
12. Cullen D, Bardhan KD, Eisner M, Kogut DG, Peacock RA, Thomson JM, et al. Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. Aliment Pharmacol Ther 1998;12:135-40.
13. Yuan JQ, Tsoi KK, Yang M, Wang JY, Threapleton DE, Yang ZY, et al. Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity. Aliment Pharmacol Ther 2016;43:1262-75. http://dx.doi.org/10.1111/apt.13642
14. Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev 2002;4:CD002296. http://dx.doi.org/10.1002/14651858.CD002296
15. Klitz U, Zochling J, Schmidt WE, Braun J. Use of NSAIDs and infection with *Helicobacter pylori* - what does the rheumatologist need to know? Rheumatology (Oxford) 2008;47:1342-7. http://dx.doi.org/10.1093/rheumatology/ken123

Q:

SELF-TEST QUESTIONS

True or false?

1. The most effective method to prevent peptic ulcers induced by non-steroidal anti-inflammatory drugs is to co-prescribe an H_2-antogonist.
2. Proton pump inhibitors are more effective in preventing duodenal, rather than gastric ulcers, induced by non-steroidal anti-inflammatory drugs.

Answers on page 119

ARTICLE

Management of Bell's palsy

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Keywords
antiviral drugs, Bell's palsy, corticosteroids

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SUMMARY

Bell's palsy is facial nerve paralysis of unknown cause. Left untreated, 70–75% of patients make a full recovery.

Early treatment with prednisolone increases the chance of complete recovery of facial function to 82%. Eleven people need to be treated for one extra complete recovery at six months.

There may be benefit in adding an antiviral drug to prednisolone in some cases. Additional research is needed on this treatment.

The palsy may leave the surface of the eye exposed. Early eye protection with lubrication and a patch is crucial to prevent long-term complications.

Introduction

Bell's palsy, also called idiopathic facial paralysis, is defined as an acute-onset, isolated, unilateral, lower motor neurone facial weakness. The reported annual incidence varies in different parts of the world with estimates varying between 11 and 40 per 100 000 people.[1] It is more common in people with diabetes.[2]

Aetiology

The underlying pathophysiology observed in post-mortem cases of Bell's palsy is vascular distension, inflammation and oedema with ischaemia of the facial nerve. The aetiology remains unclear. Various causes have been proposed including viral, inflammatory, autoimmune and vascular. However, reactivation of herpes simplex virus or herpes zoster virus from the geniculate ganglion is suspected to be the most likely cause.[3,4] Despite advances in neuroimaging, the diagnosis of Bell's palsy is mainly clinical.[5]

Clinical features

Symptoms and signs of Bell's palsy (see Fig. and Box) can vary from mild to severe. There are several conditions to consider in the differential diagnosis:

- upper motor neurone lesion – based on innervation, absence of forehead wrinkling is a reliable way of differentiating Bell's palsy from an upper motor neuron lesion
- herpes zoster oticus (Ramsay Hunt syndrome)
- rarer causes including otitis media, HIV infection, sarcoidosis, autoimmune disorders or tumours of the parotid gland.

Complications

In addition to ocular problems, complications of Bell's palsy include:

- motor synkinesis (involuntary movement of muscles occurring at the same time as deliberate movement, e.g. involuntary mouth movement during voluntary eye closure)
- crocodile tears (tears when eating due to misdirection of regenerating gustatory fibres destined for the salivary glands, so that they become secretory fibres to the lacrimal gland and cause ipsilateral tearing while the patient is eating)
- incomplete recovery
- contracture of facial muscles
- reduction or loss of taste sensation
- problems with dysarthria due to facial muscle weakness.

Prognosis

The severity of symptoms of Bell's palsy varies from mild weakness to severe paralysis, but the prognosis is generally good. The Copenhagen Facial Nerve Study found that around 71% of patients recover normal function without treatment. Around 13% are left with slight weakness and around 4% with severe weakness resulting in major facial dysfunction. Contracture of the facial muscles on the affected side was found in 17% and associated movements were found in 16%.[6] Scoring systems such as the House–Brackmann scale used in randomised controlled trials and systematic reviews may be helpful to monitor progress.[7]

Although the study was underpowered to detect significant differences in recovery between patients with different degrees of severity, the recovery rate

in one randomised controlled trial was significantly higher for those with moderate severity at onset compared to those with severe Bell's palsy. Recovery was 90% with those moderately affected and 78% in those severely affected.[8]

The frequency of review depends on the individual patient and the severity of their symptoms. If there is no improvement after a month the patient should be referred. A referral is also indicated if there is only partial recovery after 6–9 months.

The palsy recurs in 7% of patients, with equal incidence of ipsilateral and contralateral recurrence. There are insufficient data on whether treatment affects the rate of recurrence.

Management

The treatment of Bell's palsy aims to speed recovery and reduce long-term complications. An inability to close the eye on the affected side increases the risk of corneal complications. Eye protection is crucial so an eye patch and lubricants are used to prevent drying of the cornea. Eye drops, such as hypromellose drops, should be applied for lubrication during the day and ointment at night. In severe cases, the eye may have to be taped or partially sutured shut.

Drug therapy

The treatments considered for Bell's palsy include oral corticosteroids (prednisolone) and antiviral drugs. Although the aetiology of Bell's palsy is uncertain, it is known that inflammation and oedema of the facial nerve are responsible for the symptoms. Corticosteroids have therefore been used for their anti-inflammatory effect.

Corticosteroids

The maximum benefit is seen when steroids are commenced within 72 hours of the onset of symptoms. There is no optimum regimen, but in adults 50–60 mg prednisolone daily for 10 days has been commonly used.[6,7] Prednisolone has been used at a dose of 1 mg/kg/day up to a maximum of 80 mg in some studies. Doses of more than 120 mg/day have been used safely in patients with diabetes.[9]

In a randomised controlled trial the recovery rate at nine months with prednisolone was 94%. It was 81.6% in patients who did not receive prednisolone.[7]

A systematic review of trials that used prednisolone showed that at six months 17% of patients had incomplete recovery compared with 28% of patients who received no treatment. There was also a significant reduction in motor synkinesis in those who received prednisolone. There was no significant reduction in cosmetically disabling sequelae.[10]

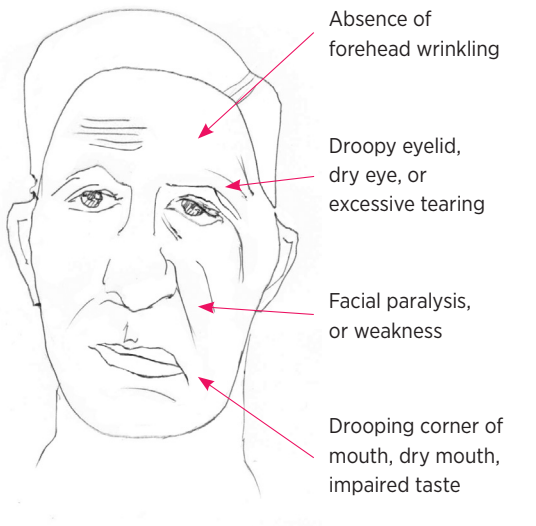
Antiviral drugs

The antiviral drugs used in trials were aciclovir (400 mg five times daily for five days) or valaciclovir (1000 mg/day for five days).[11] There is currently no evidence to support the use of either antiviral drug on its own,[12,13] and there is uncertainty regarding the benefit of adding them to corticosteroids.

Combination therapy

A randomised controlled trial found that at nine months of diagnosis, facial function had recovered in 94.4% of patients who took prednisolone alone, 85.4% of those who took aciclovir alone and 92.7%

Fig. **Possible signs of Bell's palsy**



Box **Clinical features of Bell's palsy**

Weakness or paralysis of the upper and lower facial muscles of the affected side

Drooping of ipsilateral eyelids

Inability to close the eye completely

Dry eye due to inability to close eyes completely

Excessive tearing of the eye (epiphora)

Drooping of the corner of the mouth

Ipsilateral impaired/loss of taste sensation

Difficulty with eating due to ipsilateral muscle weakness causing food to be trapped on the affected side of the mouth

Dribbling of saliva

Altered sensation on the affected side of the face

Pain in or behind the ear

Increased sensitivity to sound (hyperacusis) on affected side if stapedius muscle is involved

of those who received both. There were no serious adverse effects in any group. The study concluded that early treatment with prednisolone alone increases the likelihood of complete recovery and there was no additional benefit of treatment with aciclovir alone or combining with prednisolone.[7] However, a systematic review also found that treatment with prednisolone reduced the chances of incomplete recovery but using an antiviral drug had an additional benefit.[14]

There have been several studies looking at the benefit of antiviral drugs with or without prednisolone. A randomised prospective study found that a combination of an antiviral and a steroid was more effective in treating severe to complete Bell's palsy than steroid alone.[15] A guideline development group found that there was low-quality evidence of benefit from adding antivirals. Patients who are offered them in addition to corticosteroids should be counselled that the increase in recovery is less than 7%.[16]

A Cochrane review in 2015 found that antivirals combined with corticosteroids improved rates of incomplete recovery compared with corticosteroids alone, but this was not significant and the evidence was low quality. There was moderate-quality evidence that the combination reduced long-term sequelae such as excessive tear production and synkinesis. The outcome for patients who received corticosteroids alone was significantly better than for those who received antivirals alone. Antiviral drugs alone had no benefit over placebo. None of the treatments had significant differences in adverse effects, but the evidence was again of low quality.[12]

The optimum management of children with Bell's palsy is also unknown. A major trial (BellPIC) in Australia is addressing this question.[17]

Adverse effects of treatment

Treatment courses are short, but can cause adverse effects.

Prednisolone should be used with caution in immunosuppression and sepsis. It may lead to:

- induction or worsening of peptic ulcer disease
- hyperglycaemia especially in diabetics, however higher doses may be required in diabetes
- malignant hypertension
- hepatic and renal dysfunction.

Antiviral drugs may cause:

- nausea and vomiting
- abdominal pain
- diarrhoea
- neurological reactions – dizziness, convulsions (more common with higher doses)
- very rarely, hepatitis and jaundice.

Non-drug therapy

Physical therapies including tailored facial exercises, acupuncture to affected muscles, massage, thermotherapy and electrical stimulation have been used to hasten recovery. However, there is no evidence for any significant benefit. A Cochrane review concluded from poor-quality evidence that tailored facial exercises can help improve facial function, mainly for moderate paralysis and chronic cases. Early facial exercise may reduce recovery time, long-term paralysis and number of chronic cases.[18]

Surgical treatment to free the facial nerve has been considered. However the evidence for this procedure is of very low quality.[19-21]

Conclusion

The symptoms of Bell's palsy vary from mild to severe. The aetiology is still unclear, but it is known that the symptoms are caused by swelling and inflammation of the facial nerve. Eye protection remains crucial in preventing long-term eye complications.

Drug treatment is controversial, given that over 70% of patients will eventually recover normal facial function without treatment. Early treatment with prednisolone can hasten recovery and reduce long-term sequelae. Although the quality of evidence is low to moderate, there may be some benefit in adding antiviral drugs to prednisolone.[12] It is, however, important to discuss the harms and benefits with patients, given the potential adverse effects of prednisolone and antiviral drugs. <

Conflict of interest: none declared

REFERENCES

1. De Diego-Sastre JI, Prim-Espada MP, Fernández-García F. [The epidemiology of Bell's palsy]. Rev Neurol 2005;41:287-90.
2. Adour K, Wingerd J, Doty HE. Prevalence of concurrent diabetes mellitus and idiopathic facial paralysis (Bell's palsy). Diabetes 1975;24:449-51.
3. Linder T, Bossart W, Bodmer D. Bell's palsy and Herpes simplex virus: fact or mystery? Otol Neurotol 2005;26:109-13. http://dx.doi.org/10.1097/00129492-200501000-00020
4. Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N. Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. Ann Intern Med 1996;124:27-30. http://dx.doi.org/10.7326/0003-4819-124-1_Part_1-199601010-00005
5. Seok JI, Lee DK, Kim KJ. The usefulness of clinical findings in localising lesions in Bell's palsy: comparison with MRI. J Neurol Neurosurg Psychiatry 2008;79:418-20. http://dx.doi.org/10.1136/jnnp.2007.118489

6. Peitersen E. Bell's palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl 2002;549:4-30. http://dx.doi.org/10.1080/000164802320401694
7. Sullivan FM, Swan IR, Donnan PT, Morrison JM, Smith BH, McKinstry B, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. N Engl J Med 2007;357:1598-607. http://dx.doi.org/10.1056/NEJMoa072006
8. Sullivan FM, Swan IRC, Donnan PT, Morrison JM, Smith BH, McKinstry B, et al. A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study. Health Technol Assess 2009;13(47):1-130. http://dx.doi.org/10.3310/hta13470
9. Saito O, Aoyagi M, Tojima H, Koike Y. Diagnosis and treatment for Bell's palsy associated with diabetes mellitus. Acta Otolaryngol Suppl 1994;511:153-5.
10. Madhok VB, Gagyor I, Daly F, Somasundara D, Sullivan M, Gammie F, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2016;7:CD001942. http://dx.doi.org/10.1002/14651858.CD001942.pub5
11. Hato N, Yamada H, Kohno H, Matsumoto S, Honda N, Gyo K, et al. Valacyclovir and prednisolone treatment for Bell's palsy: a multicentre, randomized, placebo-controlled study. Otol Neurotol 2007;28:408-13. http://dx.doi.org/10.1097/01.mao.0000265190.29969.12
12. Allen D, Dunn L. Aciclovir or valaciclovir for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2004;3:CD001869. http://dx.doi.org/10.1002/14651858.CD001869.pub2
13. Gagyor I, Madhok VB, Daly F, Somasundara D, Sullivan M, Gammie F, et al. Antiviral treatment of Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2015;11:CD001869. http://dx.doi.org/10.1002/14651858.CD001869.pub8
14. de Almeida JR, Al Khabori M, Guyatt GH, Witterick IJ, Lin VY, Nedzelski JM, et al. Combined corticosteroid and antiviral treatment for Bell palsy: a systematic review and meta-analysis. JAMA 2009;302:985-93. http://dx.doi.org/10.1001/jama.2009.1243
15. Lee HY, Byun JY, Park MS, Yeo SG. Steroid-antiviral treatment improves the recovery rate in patients with severe Bell's palsy. Am J Med 2013;126:336-41. http://dx.doi.org/10.1016/j.amjmed.2012.08.020
16. Gronseth GS, Paduga R; American Academy of Neurology. Evidence-based guideline update: steroids and antivirals for Bell palsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2012;79:2209-13. http://dx.doi.org/10.1212/WNL.0b013e318275978c
17. Research Data Australia [Internet]. Bell's palsy in children (BellPIC) [2015-2020]. Australian National Data Service. https://researchdata.ands.org.au/bells-palsy-children-bellpic/518554 [cited 2017 May 1]
18. Teixeira LJ, Valbuza JS, Prado GF. Physical therapy for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2011;12:CD006283. http://dx.doi.org/10.1002/14651858.CD006283.pub3
19. McAllister K, Walker D, Donnan PT, Swan I. Surgical interventions for the early management of Bell's palsy. Cochrane Database Syst Rev 2013;10:CD007468. http://dx.doi.org/10.1002/14651858.CD007468.pub3
20. Grogan PM, Gronseth GS. Practice parameter: Steroids, acyclovir, and surgery for Bell's palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:830-6. http://dx.doi.org/10.1212/WNL.56.7.830
21. de Almeida JR, Guyatt GH, Sud S, Dorion J, Hill MD, Kolber MR, et al.; Bell Palsy Working Group, Canadian Society of Otolaryngology - Head and Neck Surgery and Canadian Neurological Sciences Federation. Management of Bell palsy: clinical practice guideline. CMAJ 2014;186:917-22. http://dx.doi.org/10.1503/cmaj.131801

ARTICLE

Changing Australian medicine names

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adrenaline (epinephrine), drug regulation, International Non-proprietary Names (INNs), medication safety

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SUMMARY

The Therapeutic Goods Administration is changing the names of approximately 200 medicines.

The aim is to harmonise Australian medicine names with international names to reduce confusion and inconsistency, which ultimately improves medication safety and the quality use of medicines.

Most of the changes will have a four-year transitional arrangement. However, a short list of medicines has seven years to transition, with a requirement for dual labelling during this period.

Adrenaline and noradrenaline are special cases and will always be known as 'adrenaline (epinephrine)' and 'noradrenaline (norepinephrine)'.

Doctors, pharmacists and other health professionals, consumers, manufacturers, sponsors and companies providing services and programs to support the prescribing and administration of medicines, need to be aware of these changes.

Introduction

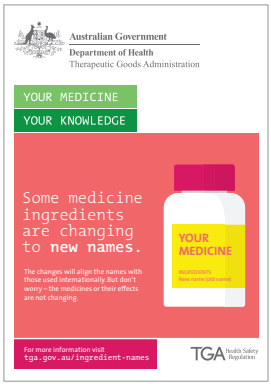
In 2013, the Therapeutic Goods Administration (TGA) announced its intentions to harmonise Australian drug names (active substance) and their excipients (inactive ingredients) with naming conventions abroad.[1] Australia has had its own system of naming drugs (Australian Approved Names – AANs). However from April 2016, the TGA has updated some medicine and ingredient names to be consistent with International Non-proprietary Names (INNs) wherever possible. The INN nomenclature system was developed by the World Health Organization (WHO) and has received Australian input. A four-year transition period will allow manufacturers, health professionals and patients to adjust to the changes.

Why are drug names being changed?

In the long term, making medicine names more consistent with nomenclature in other countries will provide clarity and reduce confusion for Australian consumers and health practitioners who travel internationally. It should also help those who trained or have practised overseas. The UK and New Zealand underwent the same process in 2003 and 2008.

The harmonisation of drug names allows the future approval of new AANs to be more closely monitored and aligned with INNs, to prevent potential confusion.

There are short-term risks to changing drug names. The Australian Bureau of Statistics reports that almost 60% of consumers have less than adequate health literacy.[2] Changes to medicine names can put people with low literacy at further risk of medication errors.



Medicines and ingredients that are affected

Approximately 200 drugs and 90 excipient names are affected, with some mentioned more than once due to having more than one salt. A full list of the affected medicines and excipients can be viewed on the TGA website.[1]

Changes to medicine names can be separated into five main categories (see Table). Adrenaline and noradrenaline have received special treatment. Due to their therapeutic use in anaphylaxis and life-threatening situations, the risk in changing the names completely to the INN nomenclature is too great in terms of safe prescribing, dispensing and administration. Adrenaline and noradrenaline will now always be known dually as 'adrenaline (epinephrine)' and 'noradrenaline (norepinephrine)'.

The transition for a selection of medicines that are either more frequently used or have a higher risk will take an additional three years, and dual labelling will be required. This will consist of the new INN name and the old approved name in parentheses afterwards. For example, 'frusemide' should be displayed as 'furosemide (frusemide)' until 2023, after which it will be just referred to as 'furosemide' (its INN nomenclature).

Many other changes are minor spelling differences or naming the hydration or salt for completeness and clarification in line with INN nomenclature. These changes will have a four-year transition period and do not require dual labelling.

Medicines and ingredients that are not affected

Some medicine names will not change because the INN is already being used in Australia. Examples include paracetamol, glibenclamide and salbutamol – in many other countries they are known as acetaminophen, glyburide and albuterol.

Communicating the changes

It is our responsibility as health professionals to convey these changes to patients to minimise confusion. The TGA has developed resources that can be displayed at GP clinics, pharmacies and hospitals to raise awareness.[3]

Who will the changes affect?

These changes go further than just affecting health practitioners and consumers. Resources such as the Australian Medicines Handbook, the Pregnancy and Breastfeeding Medicines Guide, and the Australian Injectable Drugs Handbook will need to consider the TGA's determination when reviewing their next editions.

As hospitals and health services make the transition to paperless systems and implement health information technology solutions and software, it is imperative that their service providers can show compliance with the TGA's new arrangements, as well as the national guidelines for on-screen display of clinical medicines information.[4]

On a larger scale, as state and territory governments have their own procurement and purchasing authorities, the request for tenders for the procurement of health information technology solutions must stipulate that they can comply with TGA's transitional and permanent changes with respect to medicine and excipient names.

Pharmaceutical companies that prepare medicines information will need to review the content to ensure it aligns with the updated medicine and excipient names during the transition period, and then again in 2020 or 2023 when the transitional arrangements expire.

The same goes for manufacturers of infusion pump devices, dispensing software and prescribing software companies, which will need to update their database of medicine names to comply with the TGA's new requirements. This can be an education tool for doctors and pharmacists who will see that the old name will no longer be available for selection at the point of prescribing and dispensing. It is also incumbent upon GPs and other health professionals who partake in e-health initiatives such as My Health Record and the National Prescription and Dispense Repository (NPDR) to use the correct medicine names.

Table **Examples of changes to Australian drug names**

Type of change	Current name	New name
Dual labelling until 2023	frusemide lignocaine	furosemide (frusemide) lidocaine (lignocaine)
Permanent drug labelling change	adrenaline noradrenaline	adrenaline (epinephrine) noradrenaline (norepinephrine)
Significant changes	insulin – human	insulin
Minor spelling changes	amoxycillin cephalexin cyclosporin oestradiol	amoxicillin cefalexin ciclosporin estradiol
Hydration change only	carbidopa anhydrous codeine phosphate	carbidopa codeine phosphate hemihydrate

Other TGA changes

At present, the TGA has also released new standards for labelling prescription and non-prescription medicine (TGO 91, TGO 92).[5] Over a four-year transition period, these will replace existing requirements for medicine labelling (TGO 69).[5]

The new standards have more comprehensive requirements with respect to labelling of medicines packaging. This can present a challenge to medicines with small packages or very small containers (such as vials and ampoules), and for medicines that have an expanded name due to different salts, or that require dual labelling. They have provisions and exceptions for 'small containers' and 'very small containers' which ameliorate some of these concerns.

Conclusion

The move to harmonise Australian medicine names with international names is a welcome one. Although there is likely to be some short-term disruption during the transition, the longer term benefits of improved consistency and reduced confusion align with the principles of the quality use of medicines and medication safety. ◀

Conflict of interest: none declared

REFERENCES

1. Department of Health. Therapeutic Goods Administration. Updating medicine ingredient names - list of affected ingredients [Internet]. 2016 Nov 28. Canberra: Commonwealth of Australia; 2016. www.tga.gov.au/updating-medicine-ingredient-names-list-affected-ingredients [cited 2017 May 1]
2. Australian Bureau of Statistics. Health literacy. 4102.0 - Australian Social Trends, June 2009 [Internet]. Canberra: Australian Bureau of Statistics; 2009. http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/4102.0Main+Features20June+2009 [cited 2017 May 1]
3. Department of Health. Therapeutic Goods Administration. Updating medicine ingredient names [Internet]. 2016 Nov 28. Canberra: Commonwealth of Australia; 2016. www.tga.gov.au/updating-medicine-ingredient-names [cited 2017 May 1]
4. Australian Commission on Safety and Quality in Health Care. Electronic medication management (EMM) [Internet]. Sydney: ASCQHC; 2017. https://www.safetyandquality.gov.au/our-work/medication-safety/electronic-medication-management-systems/ [cited 2017 May 1]
5. Department of Health. Therapeutic Goods Administration. Medicine labels: guidance on TGO 91 and TGO 92. 2016 Aug 17 [Internet]. Canberra: Commonwealth of Australia; 2016. www.tga.gov.au/medicine-labels-guidance-tgo-91-and-tgo-92 [cited 2017 May 1]

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ARTICLE

Genomic testing as a tool to optimise drug therapy

SUMMARY

A person's genetic make-up, including their ethnicity, can affect how they respond to a drug. It can also contribute to drug toxicity and efficacy.

Pharmacogenomic testing is now inexpensive, relatively fast and can enhance patient care.

Pre-emptive tests for azathioprine and abacavir are subsidised by Medicare.

A national regulatory system including standardised reporting and guidelines for interpreting test results is urgently needed. Improved education for GPs and pharmacists at postgraduate and undergraduate levels is also needed.

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Introduction

The effectiveness and safety of a drug dose are influenced by several patient factors including age, disease, lifestyle and concomitant drugs. Genetic factors can also play a critical role and in some cases genetic testing has become part of treatment guidelines. Tests are performed on patients' DNA from blood, saliva or buccal samples. Some of these tests are subsidised by Medicare, but many are not (see Table).

Currently most testing to optimise therapy is done to prevent severe and life-threatening adverse effects. Twenty years ago, the technology to perform rapid turnaround testing was very limited, time consuming, expensive and insufficiently specific. However, modern genetic technology makes testing feasible as it requires a very small amount of DNA, it is cheap (less than $1 per variant) and provides results quickly.

The terminology has changed from the original pharmacogenetics to pharmacogenomics. This arose with changes in technology allowing all genes to be sequenced in a single test.

Why are some drugs subject to testing?

Genetic testing can be used as a tool to optimise drug therapy. Genes control the production of proteins that metabolise and excrete drugs and transport them to their site of action in the body. Proteins are also the targets of drugs. Genes are polymorphic, meaning they have a number of variants that can lead to loss (the most common) or gain of function, or have minimal or no effect on protein function. In most cases, the clinical relevance is minor and genetic testing cannot be justified. However, for a few drugs, testing prevents life-threatening reactions in susceptible people and is recommended in routine practice.

In some ethnic populations, the frequencies of specific variant alleles are substantially different from those of Caucasians. This may affect the way patients respond to drugs such as thiopurines, allopurinol and carbamazepine, and increase their risk of severe adverse reactions.

Allopurinol

People with the human leukocyte antigen HLA-B*5801 allele given allopurinol can develop a drug reaction with eosinophilia and systemic symptoms (DRESS)[1] and Stevens-Johnson syndrome or toxic epidermal necrolysis which are severe and life-threatening. These reactions are more likely to occur within the first two months of therapy. Although the carriage of the HLA-B*5801 allele has a much higher frequency in people with Asian ancestry compared with Caucasians (5–15% vs ≤6%), it is still represented in European and African populations. In Australia, the carriage rate is about 3%.

Carbamazepine

HLA-B*1502 screening may be warranted to prevent Stevens-Johnson syndrome or toxic epidermal necrolysis associated with carbamazepine. Carriage of HLA-B*1502 is prevalent in South-East Asian and South Asian populations (10–20%) but rare in European populations (<0.1%). In 2007 the US Food and Drug Administration mandated notification of this risk in the product information for carbamazepine with a specific recommendation for HLA-B*1502 screening in South-East Asian populations.

Table **Pharmacogenomic tests in Australia**

Drug	Marker	Clinical outcome of gene variant(s)	Subsidised by Medicare	Comment
Abacavir	HLA-B*5701	Severe hypersensitivity reaction	Yes	Pharmacogenomic testing likely saved the drug from market withdrawal
Allopurinol	HLA-B*5801	Severe hypersensitivity reaction	No	Asian ancestry more vulnerable
Azathioprine	TPMT	Bone marrow suppression	Yes	Several variants need to be tested
Carbamazepine	HLA-B*1502	Severe hypersensitivity reaction	No	Asian ancestry more vulnerable
Phenytoin	CYP2C9*3	Severe hypersensitivity reaction	No	Data for Han Chinese, Japanese (strong)
	HLA-B*1502	Severe hypersensitivity reaction	No	Data for Han Chinese (weak)
	HLA-B*1301	Severe hypersensitivity reaction	No	Data for Han Chinese (weak)
Codeine	CYP2D6	Risk of respiratory depression (ultra-rapid metabolisers)	No	–
Citalopram	CYP2C19	Risk of cardiac toxicity in poor metabolisers	No	–
Clopidogrel	CYP2C19	Risk of reduced efficacy (poor metabolisers) after coronary stent placement	No	–
Interferon alfa	IL28B	Predicts response in hepatitis C	No	–
Irinotecan	UGT1A1	Gastrointestinal toxicity	No	–
Tacrolimus	CYP3A5	People with the *1/*1 genotype (CYP3A5 expressors) need up to two times the normal dose	No	Most Caucasians (>85%) have the *3/*3 genotype (CYP3A5 non-expressors) and receive the normal dose guided by therapeutic drug monitoring
Tamoxifen	CYP2D6	Risk of reduced efficacy (poor metabolisers)	No	–
Warfarin	CYP2C9/VKORC1	Elevated INR	No	–

HLA human leukocyte antigen
TPMT thiopurine methyltransferase
CYP cytochrome P450
IL interleukin
UGT uridine 5´-diphospho-glucuronosyltransferase
VKORC1 vitamin K epoxide reductase complex subunit 1

Thiopurine drugs

Thiopurine drugs are immunosuppressants used in some autoimmune and inflammatory diseases, and blood cancers. They include azathioprine, mercaptopurine and tioguanine (used in some leukaemias). These drugs can cause severe, life-threatening bone marrow suppression in 1–5% of patients on standard doses. This is due to a deficiency in thiopurine methyltransferase (TPMT) activity because of variations in the TPMT gene.

TPMT is an enzyme that metabolises thiopurine drugs. About one in 300 people have very low TPMT activity and are susceptible to this severe reaction. Bone marrow toxicity can be avoided if appropriate dosing recommendations are made based on genetic testing (see Table).

The TPMT*3C allele results in low enzyme activity. It has a frequency of almost 10% in African populations, less than 1% in Caucasians and is practically non-existent in South-East Asians.

TPMT genetic testing has been subsidised by Medicare since 2011. Most prescribers (usually hospital-based specialists) will pre-emptively order the test in patients who are likely to be prescribed thiopurine drugs.

Abacavir

The nucleoside reverse transcriptase inhibitor abacavir is indicated in HIV. A multi-organ severe hypersensitivity syndrome occurs in 5% of those prescribed abacavir. This syndrome is strongly associated with HLA-B*5701. The absence of this allele has a 100% negative

predictive value for abacavir hypersensitivity. Medicare began funding the test in 2009 and it is now routinely performed before abacavir prescription.

Phenytoin

There is an association between poor metabolisers of phenytoin (with cytochrome P450 (CYP) 2C9*3) and severe cutaneous adverse reactions such as DRESS and Stevens-Johnson syndrome or toxic epidermal necrolysis.

Citalopram

There is a risk of cardiac toxicity with citalopram in patients who are poor CYP2C19 metabolisers. The product information recommends an initial dose of 10 mg daily during the first two weeks for at-risk patients.

Codeine

There is an increased risk of respiratory depression with codeine in patients who are CYP2D6 ultra-rapid metabolisers because they rapidly and extensively convert codeine to morphine. This phenotype is mainly due to multiple CYP2D6 gene copies.

What is the evidence for pharmacogenomic testing?

In most cases, randomised clinical trials of pharmacogenomic testing have not been conducted because of cost, the drugs may be off-patent, recruitment of sufficient patients is difficult given the incidence of the drug reaction is often very low, and a perception that it is unimportant. It is more common for evidence to be based on systematic reviews and meta-analyses, with consensus statements that testing should be done because it improves safety and efficacy.

Given that testing can result in drug selection or dosage modification, it is no different from other dosing recommendations listed in the product information, such as older age, renal and hepatic dysfunctions, and drug interactions, which have rarely been the subject of randomised clinical trials.[2]

A first-of-its-kind trial conducted for abacavir showed that pre-emptive testing for HLA-B*5701 eliminated immunologically confirmed hypersensitivity to abacavir.[3] Trials of testing for CYP2C9/VKORC1 before starting warfarin had mixed results. Other studies of CYP2C19 testing before clopidogrel therapy had positive results in specific patients.

Direct-to-consumer testing

Patients can obtain their pharmacogenomic information by accessing international and Australian testing companies either directly or sometimes via a pharmacy. These companies invariably do not have specific patient details (e.g. comorbidities, severity of disease, concomitant drugs) and are limited with what recommendations can be made. The reporting back to the individual or pharmacist can be vague. For example, the report may simply state the genotype (e.g. CYP2D6*4/*4) with a simple statement of 'poor metaboliser'.

Most companies do not test the HLA alleles associated with severe adverse drug effects. Also, the drugs they recommend for dose adjustment may have been insufficiently evaluated for pharmacogenomic testing to be of value. At issue is the regulatory environment of pharmacogenomic testing and what decision support systems are in place to help doctors and patients.

Regulation and education

In Australia, the regulation of pharmacogenomic testing seems to come under the umbrella of medical devices rather than medicines at the Therapeutic Goods Administration. An overarching regulatory framework involving national regulatory bodies, with advice from professional societies, is needed to resolve critical issues. These include the need to provide broad guidance on what variant alleles should be tested, laboratory validation of the test and, more importantly, the interpretation of the test and guidelines for changing the drug or its dose. Ideally these should not be laboratory specific as is the case now. A national regulatory consensus and reporting template is warranted, so that for example a GP in Queensland will receive the same report and recommendation as a GP in Tasmania.

As genetic testing moves into mainstream medicine, there remains a clear need to improve education for GPs, specialists, pharmacists, medical students and other healthcare professionals.[4]

Conclusion

Genomic testing to optimise drug therapy is a new diagnostic tool that will increase in frequency as new discoveries are made. It will have implications for physicians, and increasingly for GPs, who coordinate patient care. In particular, pharmacogenomic testing to reduce the potential for drug-induced severe and life-threatening toxicity has immediate implications, particularly for specific ethnic groups at greater risk.[5] More drug tests will become available on Medicare once the evidence becomes established.

National regulation of pharmacogenomic testing with specific reporting and interpretation templates is needed before direct-to-consumer testing by multiple

providers creates confusion for patients and their health professionals.[6] Pre-emptive testing, companion diagnostics, point-of-care testing and decision support systems to assist doctors, patients and pharmacists need to be quickly addressed. Education for doctors and pharmacists is necessary to ensure that patients obtain their optimal pharmacotherapy based on precision medicine. ◀

Andrew Somogyi is a co-holder of a patent for a perhexiline formulation. He receives funding from the National Health and Medical Research Council (NHMRC).

*Elizabeth Phillips is a co-director of IIID Pty Ltd that holds a patent for HLA-B*5701 testing. She receives funding from the NHMRC, Australian Centre for HIV and Hepatitis Virology Research, and National Institutes of Health (1P50GM115305-01, 1R01AI103348-01, 1P30AI110527-01A1).*

REFERENCES

1. Mugwagwa AN, Fischer R, Zailan I. HLA-B*5801: a genetic susceptibility to allopurinol-induced DRESS. Med J Aust 2016;204:159-60. http://dx.doi.org/10.5694/mja15.01113
2. Pirmohamed M, Hughes DA. Pharmacogenetic tests: the need for a level playing field. Nat Rev Drug Discov 2013;12:3-4. http://dx.doi.org/10.1038/nrd3921
3. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al.; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568-79. http://dx.doi.org/10.1056/NEJMoa0706135
4. Nickola TJ, Green JS, Harralson AF, O'Brien TJ. The current and future state of pharmacogenomics medical education in the USA. Pharmacogenomics 2012;13:1419-25. http://dx.doi.org/10.2217/pgs.12.113
5. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature 2015;526:343-50. http://dx.doi.org/10.1038/nature15817
6. Caudle KE, Dunnenberger HM, Freimuth RR, Peterson JF, Burlinson JD, Whirl-Carillo M, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med 2017;19:215-23. http://dx.doi.org/10.1038/gim.2016.87

FURTHER READING

Liew D, Keith C, Booth J, Perera D. Medicinal mishap: Fatal azathioprine toxicity. Aust Prescr 2017;40:109. http://dx.doi.org/10.18773/austprescr.2017.035

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Testing for coeliac disease

SUMMARY

Coeliac disease is an immune-mediated condition in which the intestinal mucosa is damaged by exposure to gluten.

Up to 50% of people with coeliac disease are asymptomatic. A high index of suspicion is therefore required especially in at-risk groups.

Serological investigation alone is insufficient to make the diagnosis. Up to 5% of patients with coeliac disease can have negative serology.

Genotype testing for coeliac disease is most useful in the exclusion of coeliac disease. A positive test does not confirm the diagnosis.

Definitive diagnosis requires gastroscopy and duodenal biopsy. An empirical trial of a gluten-free diet has no role in the diagnosis of coeliac disease.

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Keywords
coeliac disease, gluten, serological testing

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Introduction

Coeliac disease is an immune-mediated condition that occurs in people who are genetically susceptible. There is an abnormal response to dietary gluten resulting in inflammation and damage to the small bowel mucosa. Approximately 1 in 70 Australians have coeliac disease, however it is suspected that only 20% of people with the disease are diagnosed.[1] Typical symptoms include fatigue, diarrhoea and weight loss, but up to 50% of patients with coeliac disease are asymptomatic.[2] Untreated coeliac disease can lead to complications that include early onset osteoporosis, nutrient deficiencies, infertility and malignancy. The only currently available treatment for coeliac disease is a lifelong, strict gluten-free diet.

Pathogenesis

The toxic proteins that cause coeliac disease are derived from gluten present in wheat, rye, barley and oats. They induce an immune response that results in the typical histological features of coeliac disease. These include loss of the intestinal villi (villous atrophy) and histological evidence of inflammation (crypt hyperplasia and intraepithelial lymphocytosis). The immune response produces circulating antibodies that can be measured in the serum. More than 99% of patients with coeliac disease have a genetic predisposition in the human leukocyte antigen HLA-DQ2 and DQ8. Importantly, approximately half of the Australian population carry the genes, so they are not markers for coeliac disease.

There continues to be uncertainty about oats which contain the protein avenin (a gluten protein) which can cause small bowel mucosal damage in some people with coeliac disease. Complicating this issue is that oats are commonly processed in the same environment as wheat-containing products with the consequent risk of cross-contamination. Based on current recommendations, oats should not be consumed on a gluten-free diet.

Non-coeliac gluten sensitivity is a separate clinical entity. It describes the patients who report gastrointestinal symptoms that improve on exclusion of gluten from the diet but who have no demonstrable small bowel mucosal damage when exposed to gluten. The likely cause of these symptoms is that most foods that contain gluten also contain fermentable carbohydrates such as fructans. Fermentation of these carbohydrates by colonic bacteria can result in symptoms that are very similar to those experienced in coeliac disease. This reinforces the concept that improvement in gastrointestinal symptoms after exclusion of gluten from the diet cannot be relied on as a diagnostic tool in the evaluation of potential coeliac disease.

Clinical features

The symptoms of coeliac disease vary markedly from person to person, and up to 50% of people are asymptomatic. While coeliac disease has traditionally been thought of as a condition of malnutrition and wasting, it is clear that the epidemiology has changed. In population studies, people with coeliac disease could not be identified by their weight or symptoms.[3,4]

Clinical features, if present, can include:

- gastrointestinal symptoms (diarrhoea, constipation, bloating, abdominal pain, nausea, mouth ulcers)
- weight loss
- lethargy
- infertility, miscarriages and amenorrhoea
- vitamin and mineral deficiencies (B_{12}, vitamin D, iron, folate)
- abnormal liver function tests
- early onset osteoporosis.

Associated conditions

There are associated conditions which increase the risk of the patient having coeliac disease. The clinician should have a high index of suspicion for coeliac disease if the patient has:

- a family history of coeliac disease (10% risk in first-degree relatives)
- type 1 diabetes
- autoimmune thyroid disease, Addison's disease, Sjogren's syndrome, autoimmune liver disease
- dermatitis herpetiformis
- IgA deficiency (seen in 3–5% of patients with coeliac disease)
- Turner syndrome
- Down syndrome.

Indications for testing

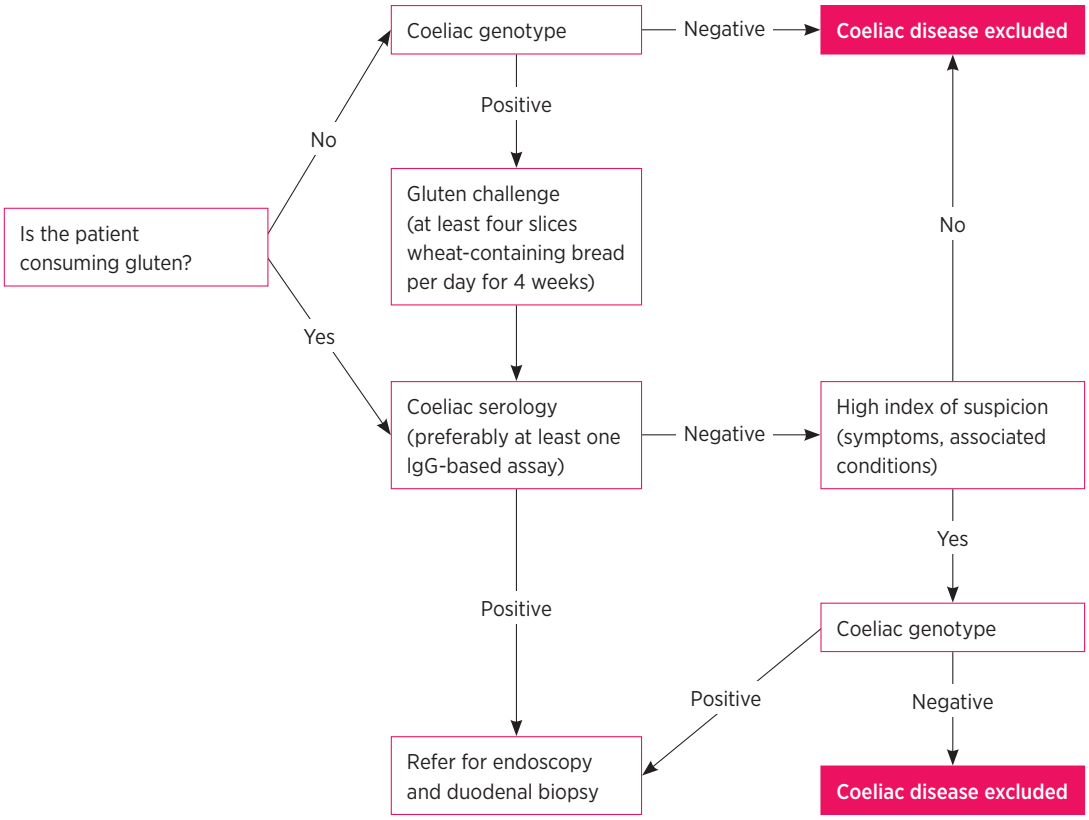
Many patients are asymptomatic or have very few symptoms and thus a high index of suspicion is required. Those with any symptoms suggestive of coeliac disease should be tested. Asymptomatic people who are first-degree relatives of those diagnosed or who have any of the associated conditions should be screened with serological testing.[5]

If serology is negative, but there is a high index of suspicion, further testing should be performed. If serology is positive the diagnosis is confirmed by endoscopy with small bowel biopsy (see Fig.).

Laboratory testing

Serological testing for coeliac disease requires the patient to be consuming a diet containing gluten at the time of testing. Before testing it is therefore important to clarify dietary gluten consumption. If the person being tested has limited or no gluten consumption then there needs to be a 'gluten challenge' with

Fig. **Diagnosis of coeliac disease**



at least four slices of wheat-containing bread per day for at least four weeks before testing. Patients undertaking a gluten challenge commonly experience some gastrointestinal symptoms but these symptoms are often short lived (often limited to 2–3 days). Importantly, the development of symptoms in response to the gluten challenge is insufficient and inaccurate in diagnosing coeliac disease. Conversely, relief of symptoms in response to a gluten-free diet has no role in diagnosis. If there are patient concerns about gastrointestinal symptoms that will develop due to a gluten challenge, suggesting a gluten-containing product with less fermentable sugars (such as spelt flour-based breads) can help reduce the symptoms.

Coeliac antibodies

Most serological screening tests for coeliac disease use either IgA or IgG antibodies. Many Australian laboratories test for both an IgA and IgG coeliac specific antibody (see Table).[2,6] This is important, because approximately 3–5% of patients with coeliac disease have IgA deficiency so testing for an IgA coeliac specific antibody alone would be unreliable in these patients.[1] Many laboratories therefore also measure total IgA to aid in interpretation. In addition, IgA coeliac antibody testing is unreliable in children less than four years of age due to immaturity of the immune system.

Antibody testing has a high sensitivity and specificity. However, false negative and false positive tests occur in approximately 5% of tests. The prevalence of seronegative coeliac disease is estimated at up to 5% of those diagnosed.[7]

Genotype testing

The Australian Coeliac Society has produced recommendations on the use of genotype testing in coeliac disease.[8] The greatest value in testing for the HLA-DQ2/DQ8 haplotype is to exclude coeliac disease. More than 99% of patients with coeliac disease will test positive for HLA-DQ2/DQ8, thus a negative test effectively excludes coeliac disease. A positive test is not helpful in diagnosing coeliac disease as 30–50% of the population carry the genes and only 10% of people who test positive will actually have coeliac disease.[9]

A specific scenario where genotype testing can be helpful is in the patient who has already commenced a gluten-free diet. If the genotype testing is negative, then coeliac disease can be confidently excluded, whereas a positive test indicates the need for formal testing after a gluten challenge.

Genotype testing can also be helpful to exclude coeliac disease when the diagnosis of coeliac disease is in doubt, such as when small bowel histology or coeliac antibody testing is equivocal. A positive genotype test in the setting of a negative small bowel biopsy and negative serology on a gluten-containing diet indicates that the patient has a genetic susceptibility but no current coeliac disease.[9]

Endoscopy and histology

Prescribing a gluten-free diet should not be taken lightly. The diet is expensive, socially isolating and there is some evidence that questions the nutritional adequacy of a gluten-free diet when used in conditions other than coeliac disease. Given the false–positive rate with serology, commencing a strict life-long gluten-free diet is not recommended without a definite diagnosis of coeliac disease. A gastroscopy for small bowel (duodenal) biopsy is the gold standard and is recommended for all patients to confirm the diagnosis. It is generally a well-tolerated procedure with few risks.

Adults with elevated coeliac antibodies should be referred for endoscopy. Patients with normal concentrations of antibodies but in whom there is a high clinical suspicion of coeliac disease should also be referred for endoscopic evaluation. As with coeliac antibodies, the specific changes associated with coeliac disease will only be present on histology if the patient is consuming a gluten-containing diet.

Histology of the small bowel in untreated coeliac disease shows intraepithelial lymphocytosis and villous atrophy of varying severity. Other causes of intraepithelial lymphocytosis and villous atrophy on small bowel biopsies include infectious gastroenteritis, giardiasis, Crohn's disease, tropical sprue, and use of non-steroidal anti-inflammatory drugs.

In children, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition has proposed that a tissue diagnosis can be avoided in specific circumstances. These are when there are signs and symptoms of coeliac disease and a high titre of coeliac specific antibodies (10 times the

Table **Serological markers for coeliac disease**

Test	Sensitivity	Specificity
Deamidated gliadin peptide (IgA)*	94–96%	95%
Deamidated gliadin peptide (IgG)	89–99%	96%
Anti-tissue transglutaminase antibodies (IgA tTG)*	80–100%	83–100%
Anti-tissue transglutaminase antibodies (IgG tTG)	90–98%	95–96%

* Measure total IgA to ensure patient is not IgA deficient.
Source: Adapted from references 2 and 6

upper limit of normal) and an at-risk genotype (HLA-DQ2/DQ8 haplotype). This proposal is controversial and we still recommend referral to a paediatric gastroenterologist before starting a gluten-free diet in these children.

Tests if a diagnosis of coeliac disease is confirmed

Screen and treat nutrient deficiencies and other complications:

- check iron, B_{12}, vitamin D, calcium and folate and treat if low
- evaluate bone mineral density
- screen for other associated conditions if clinically relevant (type 1 diabetes, autoimmune thyroid disease, liver function)
- review immunisation status (particularly consider pneumococcal vaccination as infection with this organism is higher in patients with coeliac disease, probably secondary to functional hyposplenism)
- screen first-degree relatives.

Monitoring

In addition to clinical assessment and checking the resolution of symptoms, tests are used for assessing the response to a gluten-free diet:

- check antibody concentrations – these should start to fall by 3–6 months but can remain elevated (even despite adequate dietary adherence)
- check adherence – persistently elevated antibodies or ongoing gastrointestinal symptoms should prompt referral to a dietitian for assessment of adherence and reinforcement of advice
- repeat endoscopy and small bowel biopsy after 12–24 months of a gluten-free diet, particularly if there are ongoing symptoms or if coeliac antibodies remain elevated
- review symptoms, serology, liver function and thyroid function tests annually
- test bone mineral density in all patients every two years.

Conclusion

Coeliac disease is an immune-mediated condition causing small bowel mucosal damage in genetically susceptible individuals exposed to gluten derived from wheat, rye and barley. Most tests for coeliac disease require the patient to be consuming a gluten-containing diet at the time of testing.

Although genotype testing can be performed on a gluten-free diet, it is most useful in excluding rather than confirming the diagnosis of coeliac disease. Importantly, a symptomatic response to a gluten challenge or withdrawal of gluten from the diet is insufficient and inaccurate for a diagnosis. A tissue diagnosis from duodenal histology obtained at the time of gastroscopy remains the gold standard for diagnosing coeliac disease. <

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. The diagnosis of coeliac disease can be confirmed if the patient's symptoms respond to a gluten-free diet.

4. The diagnosis of coeliac disease can be confirmed by identifying the presence of the HLA-DQ2/DQ8 haplotype.

Answers on page 119

REFERENCES

1. Kumar V, Jarzabek-Chorzelska M, Sulej J, Karnewska K, Farrell T, Jablonska S. Celiac disease and immunoglobulin A deficiency: how effective are the serological methods of diagnosis? Clin Diagn Lab Immunol 2002;9:1295-300. http://dx.doi.org/10.1128/CDLI.9.6.1295-1300.2002
2. Hill ID. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? Gastroenterology 2005;128 Suppl 1:S25-32. http://dx.doi.org/10.1053/j.gastro.2005.02.012
3. Rosén A, Sandström O, Carlsson A, Högberg L, Olén O, Stenlund H, et al. Usefulness of symptoms to screen for celiac disease. Pediatrics 2014;133:211-18. http://dx.doi.org/10.1542/peds.2012-3765
4. van der Pals M, Myléus A, Norström F, Hammarroth S, Högberg L, Rosén A, et al. Body mass index is not a reliable tool in predicting celiac disease in children. BMC Pediatr 2014;14:165. http://dx.doi.org/10.1186/1471-2431-14-165
5. Fasano A, Catassi C. Clinical practice. Celiac disease. N Engl J Med 2012;367:2419–26. http://dx.doi.org/10.1056/NEJMcp1113994
6. Sblattero D, Berti I, Trevisiol C, Marzari R, Tommasini A, Bradbury A, et al. Human recombinant tissue transglutaminase ELISA: an innovative diagnostic assay for celiac disease. Am J Gastroenterol 2000;95:1253-7. http://dx.doi.org/10.1111/j.1572-0241.2000.02018.x
7. Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut 2014;63:1210–28. http://dx.doi.org/10.1136/gutjnl-2013-306578
8. Tye-Din JA, Cameron DJ, Daveson AJ, Day AS, Dellsperger P, Hogan C, et al. Appropriate clinical use of human leukocyte antigen typing for coeliac disease: an Australasian perspective. Intern Med J 2015;45:441-50. http://dx.doi.org/10.1111/imj.12716
9. Anderson RP, Henry MJ, Taylor R, Duncan EL, Danoy P, Costa MJ, et al. A novel serogenetic approach determines the community prevalence of celiac disease and informs improved diagnostic pathways. BMC Med 2013;11:188. http://dx.doi.org/10.1186/1741-7015-11-188

FEATURE

Medicinal mishap

Fatal azathioprine toxicity

Case

A 59-year-old female underwent a renal transplant in early 2015. Her initial immunosuppression regimen was mycophenolate mofetil, prednisolone and tacrolimus. The post-transplant recovery was complicated by chronic diarrhoea. This was related to mycophenolate and occurred with both the mofetil and the sodium salts.

In January 2016, while the patient was overseas, her diarrhoea worsened. She was admitted to hospital where mycophenolate sodium was stopped and azathioprine was started.

When assessed back in Australia, one month after starting azathioprine, the patient was found to have severe pancytopenia and she was admitted to hospital. The azathioprine was stopped, but the pancytopenia persisted despite three weeks of treatment with filgrastim and blood products. It was complicated by febrile neutropenia and polymicrobial sepsis. The patient died one month after admission from multi-organ failure secondary to bone marrow failure.

Comment

Azathioprine, a prodrug of mercaptopurine, is a purine antimetabolite which suppresses the immune system. In addition to preventing the rejection of organ transplants, it can be used to manage a range of autoimmune and inflammatory conditions such as inflammatory bowel disease and systemic lupus erythematosus.

The enzyme thiopurine methyltransferase (TPMT) is important for converting azathioprine and mercaptopurine into inactive metabolites. This reduces the consequent risk of myelosuppression. In 0.3–0.6% of Caucasians there are genetic polymorphisms that lead to markedly reduced TPMT activity.[1] During her final admission our patient was found to have a genetic polymorphism, which resulted in low TPMT activity. This made her extremely sensitive to the myelosuppressive effects of azathioprine.

The role of genetic testing is uncertain. Pathology laboratories often report intermediate-activity genetic polymorphisms, however the clinical implications of this result are unclear. TPMT activity can also be quantified by directly testing the enzyme's activity (often described as a TPMT phenotype). While this method should capture all patients with low TPMT activity, the result is subject to significant intra-individual variability.[2] Either method of testing is practically effective in detecting patients with low enzyme activity. An alternative approach to the patient taking azathioprine is to frequently monitor the full blood count, looking for the onset of neutropenia.

Recommendations

This case highlights that low TPMT activity, although uncommon, can have fatal consequences, particularly if there are inadequate blood counts in patients taking azathioprine. Routine testing may be useful in predicting an individual patient's risk of myelosuppression, as well as adjusting dosing.[3] It is easy to incorporate into standard practice, and is likely to have a favourable cost–benefit profile.[4]

We recommend that TPMT testing should be strongly considered before starting azathioprine. Azathioprine use can usually be anticipated so testing should be done before the patient starts the drug.

TPMT testing identifies a large proportion, but not all, of patients at risk of severe myelosuppression. Patients taking azathioprine should therefore have regular full blood counts, particularly during the first three months of therapy (at least weekly).

We would like to acknowledge the patient's family for permitting use of this case.

David Liew is attending Editorial Executive Committee meetings as the clinical pharmacology registrar for Australian Prescriber *in 2017.*

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REFERENCES

1. Australian medicines handbook. Adelaide: Australian Medicines Handbook; 2017. https://amhonline.amh.net.au [cited 2017 May 1]
2. Lennard L, Cartwright CS, Wade R, Richards SM, Vora A. Thiopurine methyltransferase genotype–phenotype discordance and thiopurine active metabolite formation in childhood acute lymphoblastic leukaemia. Br J Clin Pharmacol 2013;76:125-36. http://dx.doi.org/10.1111/bcp.12066
3. Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, Yee SW, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther 2011;89:387-91. http://dx.doi.org/10.1038/clpt.2010.320
4. Ford LT, Berg JD. Thiopurine S-methyltransferase (TPMT) assessment prior to starting thiopurine drug treatment; a pharmacogenomic test whose time has come. J Clin Pathol 2010;63:288-95. http://dx.doi.org/10.1136/jcp.2009.069252

BOOK REVIEW

Book review

Therapeutic Guidelines: Palliative Care. Version 4.

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Aust Prescr 2017;40:110
http://dx.doi.org/10.18773/austprescr.2017.032

Melbourne: Therapeutic Guidelines Limited; 2016. 393 pages
Also available online at www.tg.org.au

A practical and up-to-date Australian palliative care text for all healthcare professionals, particularly those working in primary care, is vital. The revised (4th edition) Therapeutic Guidelines: Palliative Care continues to provide good advice from expert clinicians on a range of practical issues, including symptom management, communication guidance and support for deprescribing.

Advance care planning is a significant component of palliative care and a new stand-alone chapter on this is welcomed. While the advance care planning guidance is general in nature, clinicians will appreciate the text's practical suggestions of approaching conversations about death and dying. These practical examples continue throughout the text, including 'Loss, grief and bereavement' and the revised chapter on 'Terminal care: care in the last days of life'. Clinicians will welcome this.

A palliative approach to care often necessitates changes in the way comorbidities are managed. The new chapter 'Managing comorbidities and deprescribing in palliative care' provides general advice on management. While abrupt withdrawal of medicines is discussed, specific recommendations for managing this situation are lacking.

The revised version sensibly lists resources within each chapter, rather than as an appendix. Furthermore, the online version provides hyperlinks to web-based resources. At first glance, the hyperlinks to the Australian Pharmaceutical Benefits Scheme (PBS) appear helpful, however they take the clinician to pages that may be irrelevant to the specific indication, patient group, route of administration, and formulation or dose provided within the prescribing guidance. In fact, the drug may not be subsidised by the PBS. This will frustrate clinicians as it affects a number of drugs, including midazolam, gabapentin, glycopyrrolate and fentanyl.

This updated text contributes to the contemporary multidisciplinary practice of palliative care within an Australian context. It will appeal in particular to the needs of clinicians working in primary care.

BOOK REVIEW

Book review

Therapeutic Guidelines: Gastrointestinal. Version 6.

Melbourne: Therapeutic Guidelines Limited; 2016.
269 pages
Also available online at www.tg.org.au

The latest version of the gastrointestinal guideline is concise and practical. In light of new evidence, it has additional sections on topics such as the oral direct-acting antiviral regimens for hepatitis C. There is also helpful guidance on treatment options for irritable bowel syndrome and the different types of food intolerance. There are new sections on parenteral nutrition and more specific information on refeeding syndrome.

In my role as a general practice registrar, I refer to this book almost daily. The information is presented in an easy-to-read format by using tables and summaries. In terms of prescribing pharmacotherapy, the book gives up-to-date doses and duration of use in accordance with current guidelines.

I recommend this updated version to any clinician working in a hospital or the community. The book, although small in size, covers common presentations of gastrointestinal diseases almost completely.

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NEW DRUGS

New drugs

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First published 10 May 2017

Brivaracetam

Approved indication: epilepsy
Briviact (UCB)
25 mg, 50 mg film-coated tablets, oral solution containing 10 mg/mL
Australian Medicines Handbook section 16.1.3

Temporal lobe epilepsy is the most common of the partial epilepsies. Carbamazepine is generally considered the first-line drug for managing partial epilepsy, but it may not completely control seizures. There are many antiepileptic drugs which can be added such as gabapentin, lamotrigine and levetiracetam. Brivaracetam is another add-on therapy for adults with partial-onset seizures, with or without secondary generalised seizures.

Brivaracetam is thought to act on a protein (SV2A) in the synaptic vesicles. By binding to this protein the drug is thought to alter the release of neurotransmitters into the synapse. The reduction in seizures is proportional to the concentration of brivaracetam in plasma.

It is recommended to begin treatment with 100 mg doses (50 mg twice daily) then adjust the dose according to the response. The tablets are completely absorbed and brivaracetam rapidly enters the brain. Its half-life is about nine hours with most of the dose being metabolised and excreted in the urine. Dose adjustments may be necessary for patients with hepatic impairment and the drug should be avoided in patients with end-stage renal disease on dialysis due to a lack of data. Plasma concentrations of brivaracetam are reduced if it is taken with carbamazepine, phenobarbital (phenobarbitone) or phenytoin.

The approval of brivaracetam is based on the results of three main trials.[1-3] The patients in these trials had partial epilepsy that was not controlled by one or two drugs. Different doses of brivaracetam were compared with placebo over 12 weeks.

One trial studied total daily doses of 5 mg, 20 mg or 50 mg in 396 patients. Only the 50 mg dose was significantly better than adding a placebo. This dose reduced weekly seizure frequency by 12.8% more than placebo.[1]

A similar trial involving 398 patients studied total daily doses of 20 mg, 50 mg and 100 mg. Respectively, these reduced weekly seizure frequency by 6.8%, 6.5% and 11.7% more than placebo. Only the 100 mg dose made a statistically significant difference.[2]

The third main trial of brivaracetam involved 768 patients and studied total daily doses of 100 mg and 200 mg. Based on the reduction in seizure frequency during the treatment period, the proportion of patients having a response of 50% or more was significantly higher with brivaracetam. This responder rate was achieved by 38.9% of the patients taking 100 mg, 37.8% of those taking 200 mg and 21.6% of the placebo group. Averaged over a 28-day period, the reduction in seizure frequency was 22.8% greater than placebo for 100 mg and 23.2% greater with 200 mg.[3]

Across the clinical trials, 6.7% of the patients taking brivaracetam discontinued it because of adverse events. Only 3.9% of the patients given a placebo discontinued. The main reasons for stopping treatment included dizziness, headache and fatigue. Other adverse events caused by brivaracetam include nausea, irritability and somnolence. Some patients become depressed and a few may develop suicidal thoughts. Pooled data suggest the incidence of suicide and suicide attempts is 3.2 per 1000 patient-years.

The clinical trials show that the percentage reduction in seizures is greater than the reduction with placebo. Based on the trial of higher doses, in which patients were having a median of 10 seizures every month, the difference between brivaracetam and placebo is probably two or three seizures per month. Few patients will stop having seizures. In the same trial 5.2% of the patients taking a total daily dose of brivaracetam 100 mg became seizure free.[3]

An attempt has been made to compare brivaracetam with levetiracetam. This indirect comparison was based on a systematic review of 13 placebo-controlled trials. There were 1919 patients in the brivaracetam trials and 1765 in the levetiracetam trials. For all doses of brivaracetam, there were no statistically significant differences in efficacy.[4] Some patients who have previously been treated with levetiracetam may respond to brivaracetam, but there is no benefit in using the drugs together.[1-3] The systematic review found that levetiracetam was less likely to cause dizziness than higher total daily doses (150 mg, 200 mg) of brivaracetam.[4]

T T manufacturer provided additional useful information

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

REFERENCES

1. Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. Epilepsia 2014;55:57-66. https://doi.org/10.1111/epi.12433
2. Ryvlin P, Werhahn KJ, Blaszczyk B, Johnson ME, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia 2014;55:47-56. https://doi.org/10.1111/epi.12432
3. Klein P, Schiemann J, Sperling MR, Whitesides J, Liang W, Stalvey T, et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia 2015;56:1890-8. https://doi.org/10.1111/epi.13212
4. Zhang L, Li S, Li H, Zou X. Levetiracetam vs. brivaracetam for adults with refractory focal seizures: a meta-analysis and indirect comparison. Seizure 2016;39:28-33. https://doi.org/10.1016/j.seizure.2016.05.004

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

NEW DRUGS

Aust Prescr 2017;40:114–5
http://dx.doi.org/10.18773/austprescr.2017.039
First published 10 May 2017

Conjugated oestrogens/bazedoxifene

Approved indication: menopause
Duavive (Pfizer)
0.45 mg/20 mg modified-release tablet
Australian Medicines Handbook section 17.2.1

This product is indicated for moderate to severe vasomotor symptoms associated with menopause in women with an intact uterus. It combines conjugated equine oestrogens with bazedoxifene, a selective oestrogen receptor modulator. Bazedoxifene has been added to inhibit the stimulating effects of oestrogens on the endometrium and reduce the risk of endometrial cancer.

A placebo-controlled trial assessed two fixed-dose combinations of conjugated oestrogens/bazedoxifene (0.45 mg/20 mg, 0.625 mg/20 mg) in women who were having at least seven moderate to severe hot flushes a day. They were aged 42–63 years with an average of 4.5 years since menopause. After 12 weeks of treatment, both doses significantly reduced the number and severity of hot flushes (see Table).[1]

In a safety cohort of 3168 women, abdominal pain was the most frequently reported adverse event (≥10%). Other common events included muscle spasms (8%), myalgia (7.9%), nausea (6.6%), diarrhoea (5.9%) and constipation (4.7%). Increases in triglycerides were quite common (1.8% of women) so annual blood monitoring should be considered.

In longer term trials (12–24 months), the 0.45 mg/20 mg dose did not appear to significantly increase bleeding events (including uterine bleeding)[2] and breast density or breast pain[3] compared to placebo. The incidence of endometrial hyperplasia was low with the 0.45 mg/20 mg dose (1/335 women) and was similar to the incidence in the placebo group (1/354 women). An increase in endometrial thickness was significantly more common with conjugated oestrogens/bazedoxifene than with placebo.[4]

Cases of pulmonary embolism, deep vein thrombosis, retinal vein thrombosis and thrombophlebitis have been reported with this drug but were rare (<1/1000). In common with other oestrogen-containing drugs, women who have had venous thromboembolism, a thrombophilic disorder, myocardial infarction or ischaemic stroke should not be prescribed this product. Other contraindications include genital bleeding, endometrial hyperplasia, a history of breast cancer or oestrogen-dependent tumours, liver disease and porphyria. The combination is not recommended in women with renal impairment.

The recommended dose is one tablet a day taken continuously. Following oral administration, maximum serum concentrations of the conjugated oestrogens are reached after 8.5 hours and maximum concentrations of bazedoxifene are reached after 2 hours. Their half-lives are 17 and 30 hours respectively. The oestrogens are eliminated in urine and most of the bazedoxifene dose is eliminated in the faeces.

Oestrogens are partially metabolised by cytochrome P450 (CYP) 3A4 so co-administration of inducers of this enzyme could potentially reduce serum concentrations of the oestrogens. Co-administration with a CYP 3A4 inhibitor had minimal impact on the drug's pharmacokinetics. Bazedoxifene is metabolised by uridine diphosphate glucuronosyltransferase therefore concomitant drugs that induce this enzyme (e.g. rifampicin, phenytoin) may reduce bazedoxifene concentrations and increase the risk of endometrial hyperplasia. Drugs such as ibuprofen, atorvastatin and azithromycin do not appear to interact with bazedoxifene.

This oestrogen/bazedoxifene combination is effective for reducing vasomotor symptoms in postmenopausal women compared to placebo. However, it is

Table **Efficacy of conjugated oestrogens/bazedoxifene for vasomotor symptoms associated with menopause**

Oestrogens/bazedoxifene daily dose or placebo (randomised women)	Mean number of moderate–severe hot flushes/day		Mean severity score of hot flushes/day *	
	baseline	12 weeks	baseline	12 weeks
0.45 mg/20 mg (133)	10.3	2.8	2.3	1.4
0.625 mg/20 mg (133)	10.4	2.4	2.3	-
placebo (66)	10.5	5.4	2.3	2

* severity score for mild hot flush = 1, moderate hot flush = 2, severe hot flush = 3
Source: Reference 1

unclear how its efficacy will compare to oestrogen/progestogen combinations. The European Medicines Agency concluded that this product should be reserved for women who cannot take oestrogen/progestogen combinations. Data on the use of this drug for longer than two years are limited. It should be used for the shortest duration possible with regular patient monitoring.

T T manufacturer provided additional useful information

REFERENCES

1. Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized controlled trial. Menopause 2009;16:1116-24. http://dx.doi.org/10.1097/gme.0b013e3181a7df0d
2. Archer DF, Lewis V, Carr BR, Olivier S, Pickar JH. Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. Fertil Steril 2009;92:1039-44. http://dx.doi.org/10.1016/j.fertnstert.2009.05.093
3. Pinkerton JV, Harvey JA, Pan K, Thompson JR, Ryan KA, Chines AA, et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. Obstet Gynecol 2013;121:959-68. http://dx.doi.org/10.1097/AOG.0b013e31828c5974
4. Pinkerton JV, Harvey JA, Lindsay R, Pan K, Chines AA, Mirkin S, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab 2014;99:E189-98. http://dx.doi.org/10.1210/jc.2013-1707

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

NEW DRUGS

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First published 10 May 2017

Suvorexant

Approved indication: insomnia
Belsomra (Merck Sharp and Dohme)
15 mg and 20 mg tablets
Australian Medicines Handbook section 18.4

There are different patterns of insomnia, such as a delayed onset of sleep and difficulty maintaining sleep. Orexins are neuropeptides which are involved in the regulation of sleep and arousal. Orexins A and B promote wakefulness. Blocking their receptors should therefore reduce wakefulness and promote sleep. Suvorexant is the first orexin receptor antagonist to be marketed in Australia.

The drug is taken within 30 minutes of bedtime. This should be at least seven hours before the patient plans to get up again. The maximum drug concentration is reached in two hours. Suvorexant is metabolised with most of the metabolites being excreted in the faeces. Its half-life is approximately 12 hours.

Suvorexant is not recommended for patients with severe liver impairment. However, severe renal impairment has little effect on drug concentrations.

As the drug's metabolism involves cytochrome P450 3A, suvorexant should not be used with inhibitors of this enzyme system such as ciprofloxacin, clarithromycin, the azole antifungal drugs and grapefruit juice. Enzyme inducers such as phenytoin reduce the concentration of suvorexant.

In one trial of suvorexant, patients with primary insomnia were randomised to take 10 mg, 20 mg, 40 mg or 80 mg for four weeks.[1] Each group also took a placebo for four weeks. The effect of treatment was assessed by polysomnography. Sleep efficiency was defined as the ratio of the time asleep to the time spent in bed. At the start of the study, the average sleep efficiency was 66% with a total sleep time of 316 minutes. These measures improved from the first night of active treatment. After four weeks of taking suvorexant, sleep efficiency had improved by 4.7–10.4% and total sleep time had increased by 22–50 minutes.[1]

Two placebo-controlled trials randomised a total of 2030 patients with primary insomnia.[2] In the suvorexant groups 742 patients aged 18–64 years took 20 mg or 40 mg while 521 older people took 15 mg or 30 mg. The patients kept sleep diaries and had polysomnography at intervals during the three months of treatment. From the first night of treatment there was a difference in efficacy between suvorexant and placebo. After one month patients taking suvorexant (15 mg or 20 mg) were falling asleep 5–7 minutes faster and sleeping for 16–21 minutes longer compared with placebo. Similar results were seen at three months (see Table). Rebound insomnia occurred when the patients stopped suvorexant, but this was only statistically significant in one trial for patients stopping the 30 mg or 40 mg dose.[2]

A one-year trial randomised 781 patients with primary insomnia to take suvorexant or a placebo.[3] Patients over 65 years took 30 mg and other patients took 40 mg. After a year, the 322 patients still taking suvorexant either continued it or were switched to placebo. All the patients kept a diary about their sleep. At the start of the study, the patients in the placebo group said it was taking them 65 minutes to get to sleep and they slept for an average of 330 minutes. The corresponding figures for the suvorexant group were 66 minutes and 320 minutes.

Table **Three-month efficacy of suvorexant**

	Suvorexant (15 mg or 20 mg) 493 patients	**Placebo** 767 patients
Time to sleep onset		
Mean time to sleep onset at baseline	63–86 min	67–81 min
Reduction after three months	23–28 min	17–21 min
Difference from placebo at three months	6–7 min	–
Total sleep time		
Mean total sleep time at baseline	298–322 min	310–316 min
Increase after three months	51–60 min	38–41 min
Difference from placebo at three months	13–19 min	–

Source: Reference 2

When efficacy was assessed over a month the suvorexant group was getting to sleep 18 minutes sooner on average and sleeping for 39 minutes longer than before. These benefits were maintained for the patients who continued treatment for one year. There were no statistically significant differences in symptoms when suvorexant was withdrawn, but the time to sleep onset increased and the total sleep time decreased.[3]

During the one-year trial approximately 38% of the suvorexant and placebo groups did not complete the study. Adverse events caused 11.7% of the patients taking suvorexant and 8.5% of the placebo group to discontinue. Somnolence affected 13.2% of the patients taking suvorexant but only 2.7% of the placebo group. Other adverse effects which were more frequent with suvorexant were fatigue, dry mouth, dyspepsia and peripheral oedema. Although there was no overall effect on mood, four patients taking suvorexant developed suicidal ideation. Uncommon adverse effects, such as sleep walking, sleep paralysis and hallucinations, were also only reported in the suvorexant group.[3]

For a hypnotic, suvorexant has a long half-life. Although most patients are not affected, some will have residual effects the next day. They should therefore not drive or operate machinery if they are not fully alert. Alcohol and other drugs that depress the central nervous system should be avoided. The safety of suvorexant in pregnancy and lactation is unknown. Patients with neurological or psychiatric disorders were excluded from the trials.[2,3] Suvorexant is contraindicated in narcolepsy.

It should be noted that some of the clinical trials used doses that were higher than the doses approved for use in Australia (15 mg and 20 mg). The higher doses had more adverse effects, but the efficacy of suvorexant at lower doses seems modest. In a systematic review, the differences for suvorexant 15 or 20 mg compared with placebo, after three months of treatment, were six minutes for the time to fall asleep and 16 minutes for total sleep time. Thirteen patients need to be treated for one to have a 15% subjective improvement in total sleep time. As 26 would need to be treated for a 15% improvement in the time to sleep onset, this effect is not significant. The systematic review says that for every 28 people taking suvorexant 15 or 20 mg, one would experience somnolence as an adverse event.[4]

While suvorexant may be better than placebo, how it compares with other hypnotics is uncertain. Dependence is less likely to be a problem compared to benzodiazepines, but caution is advised when prescribing suvorexant to people with a history of drug abuse. If a hypnotic is required, suvorexant should not be taken for more than three months without the indication being reviewed.

T manufacturer provided the AusPAR

REFERENCES

1. Herring WJ, Snyder E, Budd K, Hutzelmann J, Snavely D, Liu K, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. Neurology 2012;79:2265-74. http://dx.doi.org/10.1212/WNL.0b013e31827688ee
2. Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. Biol Psychiatry 2016;79:136-48. http://dx.doi.org/10.1016/j.biopsych.2014.10.003
3. Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014;13:461-71. http://dx.doi.org/10.1016/S1474-4422(14)70053-5
4. Citrome L. Suvorexant for insomnia: a systematic review of the efficacy and safety profile for this newly approved hypnotic - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2014;68:1429-41. http://dx.doi.org/10.1111/ijcp.12568

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the Therapeutic Goods Administration.

NEW DRUGS

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First published 10 May 2017

Venetoclax

Approved indication: chronic lymphocytic leukaemia
Venclexta (Abbvie)
10 mg, 50 mg, 100 mg film-coated tablets

Like ibrutinib and idelalisib, venetoclax is a small-molecule oral anticancer drug that targets B-cell cancers. It works by blocking the action of the BCL2 molecule. This protein is overexpressed in chronic lymphocytic leukaemia cells and prolongs cell survival by inhibiting apoptosis.

Venetoclax is indicated for patients with relapsed or refractory chronic lymphocytic leukaemia who have the 17p genetic deletion. This mutation is associated with a poor prognosis. Venetoclax can also be given to those without the mutation if there are no other treatment options.

Venetoclax has been investigated in two published open-label trials.[1,2] An initial dose-escalation study found that when treatment was started at doses of 50 mg or more, or had been increased to 150 mg or above, tumour lysis syndrome was observed in 10 of 56 patients. One of the patients died and another developed acute renal failure. After the regimen was changed to a starting dose of 20 mg/day and more gradual titration to 400 mg/day with additional prophylaxis (e.g. hydration) and monitoring, the risk seemed to reduce. Only one of the 60 patients given the new regimen developed tumour lysis syndrome.[1]

The activity of venetoclax was studied in an uncontrolled phase II trial of 107 patients. They had previously been treated with a median of two therapies and over half of them were resistant to fludarabine or bendamustine. After a stepwise increase in the venetoclax dose from 20 mg/day to 400 mg/day over 4–5 weeks, patients were treated for a median of 12.1 months. Overall, 79 patients (74%) responded to venetoclax (based on an investigator assessment) – 17 were complete remissions (with or without recovery of blood counts), 4 were nodular partial remissions and 58 were partial remissions.[2]

Just over 40% of patients taking venetoclax developed serious neutropenia.[2] Blood monitoring is therefore recommended during treatment and the venetoclax dose should be reduced or stopped if neutropenia develops. Other common serious adverse events were infection (20%), anaemia (18%) and thrombocytopenia (15%). Milder but frequently reported events included diarrhoea (29%), nausea (28%), fatigue (22%), fever (19%), vomiting (14%) and constipation (10%).[2]

Tumour lysis syndrome occurred in 5 of 107 patients during the dose-titration phase of the efficacy trial.[2] Two of the patients had to have their treatment interrupted. Tumour lysis syndrome is more likely to occur in people with a high tumour burden. Reduced renal function also increases the risk. Monitoring of blood chemistry is recommended during treatment and venetoclax should be interrupted or stopped if tumour lysis syndrome occurs.

There were 11/107 deaths within a month of the last venetoclax dose – seven were due to disease progression, and the other four were a result of adverse events which included stroke, liver derangement, septic shock and cardiorespiratory insufficiency. None of these events was deemed to be related to venetoclax.[2]

Venetoclax tablets should be taken with food. Maximum serum concentrations are reached 5–8 hours after oral administration. The drug's elimination half-life is about 26 hours and most of the dose is excreted in the faeces.

Venetoclax is mainly metabolised by cytochrome P450 (CYP) 3A so the concomitant use of inhibitors of this enzyme (e.g. ketoconazole, clarithromycin) is contraindicated during the dose-titration phase as they may increase venetoclax concentrations. Moderate CYP3A inhibitors (e.g. erythromycin and ciprofloxacin) and P-glycoprotein inhibitors should also be avoided during the titration phase. Once a steady venetoclax dose has been reached, CYP3A inhibitors can be used but with a lower venetoclax dose. Concomitant use of CYP3A inducers (e.g. carbamazepine, rifampicin, St John's wort) should be avoided. Venetoclax could potentially affect concentrations of co-administered warfarin so close monitoring is recommended in these patients.

Although this drug is not curative, almost three-quarters of patients in the uncontrolled phase II trial responded to venetoclax. Improvements in overall survival and progression-free survival have not yet been established. Serious adverse events are common with this drug and regular blood monitoring is important.

T T manufacturer provided additional useful information

REFERENCES

1. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:311-22. http://dx.doi.org/10.1056/NEJMoa1513257
2. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label phase 2 study. Lancet Oncol 2016;17:768-78. http://dx.doi.org/10.1016/S1470-2045(16)30019-5

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At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True
3 False 4 False

Correction

Extemporaneously compounded medicines

Aust Prescr 2017;40:119
http://dx.doi.org/10.18773/austprescr.2017.042
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The article by James R Falconer and Kathryn J Steadman on extemporaneously compounded medicines (Aust Prescr 2017;40:5-8) has been corrected.

In Table 1 classifying simple versus complex compounding, the example given for simple capsules, tablets and powders was incorrect. It should have been boric acid capsules (not ethinylestradiol capsules, which are an example of complex compounding).

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