LETTERS

Letters to the Editor

Pertussis prophylaxis

Editor, – In their article on pertussis prophylaxis (Aust Prescr 2012;35:82-4) the authors recommended erythromycin 10 mg/kg (maximum 250 mg) every six hours for children aged two months or more. They make no antibiotic recommendation for children aged one month.

In 1985, good results were observed for pertussis with erythromycin estolate suspension compared to poor results with erythromycin ethyl succinate.[1] In the only randomised comparison of the two esters[2], 13 of 93 children were cured in the estolate group compared to only 4 of 97 in the ethyl succinate group (p=0.016). Ethyl succinate was given in a dose of 20 mg/kg every eight hours, which is equivalent to 15 mg/kg every six hours rather than the 10 mg/kg every six hours as recommended in the article.

Unfortunately, only erythromycin ethyl succinate suspension is available in Australia. Given the availability of azithromycin, clarithromycin and trimethoprim-sulfamethoxazole, I suggest that erythromycin ethyl succinate suspension should not be recommended for pertussis prophylaxis – and certainly not in a dose of only 10 mg/kg every six hours.

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REFERENCES

1. Bass JW. Erythromycin for pertussis: probable reasons for past failures. Lancet 1985;2:147.
2. Hoppe JE. Comparison of erythromycin estolate and erythromycin ethylsuccinate for treatment of pertussis. The Erythromycin Study Group. Pediatr Infect Dis J 1992;11:189-93.

Cheryl Jones, one of the authors of the article, comments:

Thank you to Professor Shann for his thoughtful comments about recommendations for erythromycin ethyl succinate suspension. We would like to re-emphasise the main points of our article that only under rare circumstances is antimicrobial prophylaxis indicated, as data to support efficacy and dosing are limited. Azithromycin is the preferred antibiotic for infants.

We made an error in our Table – one-month-old infants were not included. The header of the second column should read less than or equal to one month of age (≤ 1 month). The Table is based on information from the Australian Immunisation Handbook so the correct reference is reference two.[1]

The recommended dose of erythromycin 10 mg/kg (maximum 250 mg) every six hours is recommended by the Australian Immunisation Handbook[1] and other guidelines.[2,3]

We agree with the sentiment that erythromycin ethyl succinate is suboptimal for pertussis prophylaxis in infants, not only for efficacy reasons, but also for tolerability (largely gastrointestinal intolerance) and toxicity issues (pyloric stenosis in infants less than one month). Professor Shann has suggested it should not be used at all. We had recommended that its use be considered in the rare circumstances where both the use of prophylaxis is appropriate and azithromycin is not available. Arguably the assistance of public health officers in confirming the need for prophylaxis and sourcing azithromycin would be the best approach.

REFERENCES

1. Pertussis. In: The Australian Immunisation Handbook. 9th ed. Canberra: Australian Government Department of Health and Ageing; 2008. p 227-39.
2. NSW Health. Factsheet: whooping cough (pertussis). 2012. www.health.nsw.gov.au/factsheets/guideline/pertusis.html [cited 2012 Nov 8]
3. Victorian Department of Health. Pertussis (whooping cough) - advice for clinicians. 2009. http://ideas.health.vic.gov.au/diseases/pertussis.asp [cited 2012 Nov 8]

Rasagiline (Azilect)

In *Australian Prescriber's* review of rasagiline (Aust Prescr 2012;35:128-35) it is noted that:

> The Therapeutic Goods Administration originally rejected the application to register rasagiline in Australia because of an apparent increase in the risk of melanoma. However it is uncertain that the drug was responsible.

I wish to point out that it is thought that melanoma and Parkinson's disease share common genetic components.[1] Furthermore there is evidence of an association between Parkinson's disease per se and melanoma.[2] Proof of the association led the Food and Drug Administration to instigate a labelling change applicable to all dopaminergic drugs in 2007. It has also been acknowledged by the TGA and the following statement is included in the

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

Australian product information for rasagiline:

> During the clinical development program, the occurrence of cases of melanoma prompted the consideration of a possible association with rasagiline. The data collected suggests that Parkinson's disease, and not any medicinal products in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist.

In view of the evidence, Lundbeck recommends that all patients with Parkinson's disease undergo regular skin checks, including those taking rasagiline.

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REFERENCES

1. Gao X, Simon KC, Han J, Shwarzschild MA, Ascherio A. Family history of melanoma and Parkinson disease risk. Neurology 2009;73:1286-91.
2. Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between Parkinson disease and melanoma. Neurology 2011;76:2002-9.

Hypertension in pregnancy

Editor, – The article by Peter Donovan advises that ACE inhibitors and angiotensin receptor blockers are teratogenic in the first trimester of pregnancy (Aust Prescr 2012;35:47-50). These are commonly used antihypertensives which have specific benefits for individuals with chronic proteinuric renal disease and diabetes. Almost half of women aged 16–45 years attending a hypertension clinic in the UK were taking them.[1] The first ACE inhibitor, captopril, became available over 30 years ago.

Adverse fetal outcomes with ACE inhibitors in the first trimester had not been reported until a study in 2006 which described an increased risk of major cardiovascular and central nervous system congenital malformations.[2] This study however was widely criticised for unrealised confounding bias.[3] In particular, women with diet-controlled or undiagnosed diabetes were not excluded, and no adjustment was made for pre-pregnancy body mass. These are known risk factors for fetal malformations.

A subsequent study reported that ACE inhibitors in early pregnancy were associated with an increased risk of major congenital malformations, but this risk was attributable to maternal diabetes and not the drug.[4] Three more studies did not find an increased risk of major malformations with ACE inhibitors or angiotensin receptor blockers.[5-7]

The weight of evidence strongly suggests that ACE inhibitors and angiotensin receptor blockers are not teratogenic in early pregnancy, and that women of child-bearing age who may specifically benefit from their use may continue to do so while waiting to conceive.

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REFERENCES

1. Martin U, Foreman MA, Travis JC, Casson D, Coleman JJ. Use of ACE inhibitors and ARBs in hypertensive women of childbearing age. J Clin Pharm Ther 2008;33:507-11.
2. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006;354:2443-51.
3. Ray JG, Vermeulen MJ, Koren G. Taking ACE inhibitors during early pregnancy: is it safe? Can Fam Physician 2007;53:1439-40.
4. Malm H, Artama M, Gissler M, Klaukka T, Merilainen J, Nylander O, et al. First trimester use of ACE-inhibitors and risk of major malformations. Reprod Toxicol 2008;26:67.
5. Walfisch A, Al-maawali A, Moretti ME, Nickel C, Koren G. Teratogenicity of angiotensin converting enzyme inhibitors or receptor blockers. J Obstet Gynaecol 2011;31:465-72.
6. Li DK, Yang C, Andrade S, Tavares V, Ferber JR. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ 2011;343:d5931.
7. Karthikeyan VJ, Ferner RE, Baghdadi S, Lane DA, Lip GY, Beevers DG. Are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers safe in pregnancy: a report of ninety-one pregnancies. J Hypertens 2011;29:396-9.

Peter Donovan, author of the article, comments:

I agree with Dr Morton that there is increasing evidence for the safety of ACE inhibitors and angiotensin receptor blockers in the first trimester of pregnancy. The retrospective cohort study[1] provides the strongest evidence of safety thus far. Although it appears that the teratogenic effects of ACE inhibitors or angiotensin receptor blockers are unlikely to be as strong as originally suggested,[2] and may be no worse than some other drugs,[1,3] I would advocate a cautious approach.

There are alternatives for treating chronic hypertension, including nifedipine and methyldopa. There is much stronger evidence for their safety, hence they should remain first line. For women with chronic proteinuric renal disease, the harm:benefit ratio may favour the use of ongoing ACE inhibitors or angiotensin receptor blockers based on the current safety data. However, there are no data suggesting that ceasing ACE inhibitors or

LETTERS

angiotensin receptor blockers in women trying to conceive has detrimental effects on clinical endpoints, such as the need for renal replacement therapy, adverse pregnancy events or mortality.

As always, doctors should discuss all the relevant risks and benefits with the patient so she is able to make an informed decision about what is best for her and her future child. Pre-pregnancy counselling with a specialist such as an obstetric physician or obstetrician would be appropriate in these cases.

REFERENCES

1. Li DK, Yang C, Andrade S, Tavares V, Ferber JR. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ 2011;343:d5931.
2. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006;354:2443-51.
3. Mitchell AA. Fetal risk from ACE inhibitors in the first trimester [editorial]. BMJ 2011;343:d6667.

Time to restock the doctor's bag

Editor, – The *National Health Act 1953* made provisions for certain drugs to be provided to prescribers, which in turn could be provided to patients free of charge in emergency circumstances. The most recent update to this list was in May 2010, when methoxyflurane was added.

The article by John Holmes (Aust Prescr 2012;35:7-9) suggests that the list is outdated. Many drugs listed are no longer first-line treatments for specific emergencies, and special populations are not considered.

An excellent example of this is the failure to include parenteral magnesium sulfate for an eclamptic seizure. Eclampsia is uncommon with an estimated incidence of 1 in 2000 maternities. When it occurs it is associated with high maternal morbidity and mortality.

Magnesium sulfate is a safe and effective therapy that reduces morbidity and mortality when given to a pregnant woman who is fitting due to eclampsia (National Health and Medical Research Council level I evidence). Multiple high-quality systematic reviews have compared magnesium sulfate with other treatments for eclampsia such as lytic cocktail (chlorpromazine, pethidine and promethazine), diazepam and phenytoin. These trials demonstrated that magnesium sulfate was more effective than historical therapies and when compared with diazepam, it reduced the risk of maternal death.

Some drug choices do not matter, but in the case of a pregnant woman with pre-eclampsia who is fitting, giving the best available drug may save her life. Magnesium sulfate is not available in the current emergency doctor's bag. We submit that it should be.

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John Holmes, author of the article, comments:

I agree that magnesium is the treatment of choice for eclampsia. However, in my view it does not meet criteria for inclusion in the doctor's bag. Magnesium is not necessarily as safe as Drs Miles and Dennis state – excessive blood levels of magnesium may be associated with respiratory depression or cardiac conduction abnormalities. This would contravene the principles that the safety of drugs available in the doctor's bag should be commensurate with the skills of general practitioners and should be administered only in settings where there are appropriate monitoring and resuscitation facilities.

Further, it could be argued that general practitioners are highly unlikely to be treating full blown eclampsia in the community. Even in home birth situations it is likely that patients with signs of pre-eclampsia would have been transferred to hospital well before progression to convulsive eclampsia was likely.

Frusemide in the doctor's bag

Editor, – The recent article by John Holmes about the doctor's bag (Aust Prescr 2012;35:7-9) recommended that frusemide be relegated to a second- or third-line treatment in patients with acute heart failure. This recommendation is concerning and is counter to international evidence-based guidelines. Both the European Society of Cardiology[1] and the American Heart Association/American College of Cardiology guidelines[2] recommend the use of intravenous loop diuretics in acute heart failure. In line with this, the Heart Failure Society of America also recommends intravenous loop diuretics for acute pulmonary oedema.[3]

On their introduction, loop diuretics revolutionised the management of congestive cardiac failure. Their role remains important today. The recommendation against the use of frusemide as first-line treatment in acute heart failure in appropriately selected patients is potentially dangerous. Non-invasive ventilation strategies and intravenous nitrate therapy do have a role in acute heart failure. Evidence for their efficacy is largely based on studies where they were used with intravenous loop diuretics. The role of these therapies without the concomitant use of loop diuretics has not been established.[4-6]

In summary, intravenous loop diuretics remain a first-line component in the management of acute heart failure and suggestions to the contrary are not based on sound evidence nor supported by internationally recognised guidelines on the subject.

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REFERENCES

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur J Heart Fail 2008;10:933-89.
2. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACC/AHA guidelines for the diagnosis and management of heart failure in adults. J Am Coll Cardiol 2009;53:1343-82.
3. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al; Heart Failure Society of America. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010;16:e1-194.
4. Crane SD, Elliott MW, Gilligan P, Richards K, Gray AJ. Randomised controlled comparison of continuous positive airways pressure, bilevel non-invasive ventilation, and standard treatment in emergency department patients with acute cardiogenic pulmonary oedema. Emerg Med J 2004;21:155-61.
5. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 2008;359:142-51.
6. Kelly CA, Newby DE, McDonagh TA, Mackay TW, Barr J, Boon NA, et al. Randomised controlled trial of continuous positive airway pressure and standard oxygen therapy in acute pulmonary oedema. Eur Heart J 2002;23:1379-86.

John Holmes, author of the article, comments:

The mode of action of frusemide in the treatment of acute left ventricular failure is probably preload reduction. Clinical improvement is seen well in advance of its diuretic effect.[1] In this respect, frusemide is acting very similarly to nitrates. However, as mentioned in the article, there are potential adverse effects of frusemide in vascularly depleted patients and elevation of plasma renin and noradrenaline levels can exacerbate afterload, increase myocardial oxygen demand and thereby aggravate coronary ischaemia.[2] These potential effects make nitrates preferable as a first-line treatment, especially as, unlike frusemide, they have a more rapid onset of action and can be administered by intravenous infusion titrated to effect.[1,2]

My article discussed the use of emergency drugs in a general practice setting. I am therefore bemused that Drs Camuglia and Walters should criticise the established management of acute pulmonary oedema in Australian emergency departments. There is a world of difference between general practice and the management capabilities and choices available in a critical care environment. In the latter, the primary use of nitrates and non-invasive ventilation strategies in acute pulmonary oedema has been well established worldwide for over a decade.[2,3] Non-invasive ventilation in particular has been shown to reduce the need for intubation in severe acute pulmonary oedema.[4,5] Frusemide still has a role in selected cases, predominantly left-sided failure and the absence of intravascular depletion. However, the level of evidence is variously reported as II to III.

Irrespective of this, my article does not advocate removal of frusemide from the doctor's bag. However, while boluses of frusemide may be useful in a life-threatening situation outside of hospital, such treatment may be neither optimal nor appropriate in an environment where other and better therapeutic interventions are available.

REFERENCES

1. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet 1998;351:389-93.
2. Nelson GI, Silke B, Ahuja RC, Hussain M, Taylor S. Haemodynamic advantages of isosorbide dinitrate over frusemide in acute heart-failure following myocardial infarction. Lancet 1983;1:730-3.
3. Crane SD. Epidemiology, treatment and outcomes of acidotic, acute, cardiogenic pulmonary oedema presenting to an emergency department. Eur J Emerg Med 2002;9:320-4.
4. Peter JV, Moran JL, Phillips-Hughes J, Graham P, Bersten AD. Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema. Lancet 2006;367:1155-63.
5. Masip J, Roque M, Sanchez B, Fernandez R, Subirana M, Exposito J. Non-invasive ventilation in acute cardiogenic pulmonary edema. JAMA 2005;294:3124-30.