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Letters to the Editor

Cardiovascular drugs in older people

Editor, – The article on cardiovascular drugs in older people (Aust Prescr 2013;36:190-4) did not provide up-to-date evidence regarding the use of anticoagulants in older people. The elderly with atrial fibrillation are at the greatest risk of stroke.[1,2] Risk from falls has been an excuse not to treat. It is estimated that patients with atrial fibrillation, with an average stroke risk of 5% a year, would have to fall approximately 300 times in a year for the risk to outweigh the benefit.[3]

In people aged 75 years and over with atrial fibrillation, the risk of stroke may be greater than 20% a year and can be reduced to less than 5%.[4,5] In the ARISTOTLE trial,[5] apixaban was compared to warfarin in 18 201 patients. In the 5678 patients aged 75 and older, the rate of stroke or systemic embolism per year was only 1.6–2.2%. There was significantly less intracranial haemorrhage with apixaban.

Aspirin as a single drug may be marginally better than placebo, but with the risk of bleeding.[6] Aspirin plus clopidogrel is better than aspirin alone, but the risk of bleeding is similar to warfarin.[7] We agree with both the Canadian Cardiovascular Society and the European Society of Cardiology who no longer recommend antiplatelet therapy as first line in stroke prevention, irrespective of age, in patients with atrial fibrillation and a $CHADS_2$ score of at least one.[8,9]

Anticoagulants for stroke prevention in the elderly with atrial fibrillation are indicated in most patients, even if they are frail. Antiplatelet drugs are markedly inferior with similar or greater bleeding risk.[6,10,11]

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Vasi Naganathan, the author of the article, comments:

The letter raises an important question about the effectiveness and safety of anticoagulants for atrial fibrillation in older people. The authors are correct in their assertion that the evidence from clinical trials shows that anticoagulants are more effective than antiplatelets and have a similar low bleeding risk in the kind of older people who participate in clinical trials. The key question, however, is whether anticoagulants do more good than harm in older people who are frail, have multiple comorbidities and frequent falls. We do not have direct evidence about the efficacy or safety in this group because the inclusion and exclusion critera in anticoagulant trials exclude most of them.

In the ARISTOTLE trial,[1] exclusion criteria included increased bleeding risk believed to be a contraindication to oral anticoagulation, severe comorbid condition with a life expectancy of less than one year, severe renal insufficiency and inability to comply with INR monitoring. Over 80% of the

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patients in the BAFTA trial[2] were taking warfarin or aspirin before enrolment, which means the trial selected individuals who had already survived exposure to drugs that increase the risk of bleeding. In the much smaller WASPO trial[3] which specifically enrolled octogenarians, people were excluded if they had had one or more falls within the last 12 months or a Mini-Mental State Examination (MMSE) score <26.

The assertion that a patient with atrial fibrillation must have 300 falls a year before the risk of warfarin outweighs the benefit comes from a Markov decision analysis that assumed participants had no disability at all before anticoagulation. It did not take into account the fact that patients who fall often have other risks for bleeding that can lead to major bleeds other than subdural haematomas.[4]

Unless someone is brave enough to do the definitive trial that specifically looks at anticoagulation in older patients with atrial fibrillation who are truly frail, have comorbidities and are at risk of falling, or we have anticoagulation registries that include these kind of patients, we are left making clinical decisions in an 'evidence-free zone' and we will continue to see a wide variation in clinical practice.

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Classifying drugs in pregnancy

Editor, – With regard to the editorial 'Classifying drugs in pregnancy' (Aust Prescr 2014;37:38-40), we would like to comment on the statement that 'topical or inhaled exposures are generally less concerning than oral or parenteral ones'. While this is an accepted generalisation, important exceptions should be highlighted including topical retinoids and cytotoxics, as well as transdermal opioid patches.

According to several resources, topical tretinoin and isotretinoin (Australian category D) are not recommended during pregnancy.[1-4] The Australian Medicines Handbook states that 'although absorption via skin is minimal, in view of the teratogenicity of systemic retinoids, topical retinoids should not be used in pregnancy'. This is in line with the manufacturers' recommendations.

Topical 5-fluorouracil cream (Australian category D) is another important example. Spontaneous abortion and two cases of malformations in infants exposed in utero due to maternal application of the cream have been reported.[1]

Safety concerns of using transdermal fentanyl patches (Australian category C) during pregnancy should also be considered as the patch is designed to provide equivalent serum concentrations to parenteral formulations. The product information for Durogesic states that 'neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of Durogesic during pregnancy'.

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Debra Kennedy, the author of the editorial, comments:

While Felicity Prior and Kate O'Hara have listed the exceptions to my statement that 'topical or inhaled exposures are generally less concerning than oral or parenteral ones', I do not feel this adds much to the broader debate about the pros and cons of drug classification in pregnancy. In fact, many of their statements actually highlight my contention that narrative labelling rather than simple categorisation is a more effective way of outlining the risks and that this needs to be made in an appropriate clinical context.

While they acknowledge that absorption of retinoids 'via skin is minimal', they then quote the somewhat contradictory Australian Medicines Handbook recommendations that 'topical retinoids should not be used in pregnancy in view of the teratogenicity of systemic retinoids'. Clearly if a woman is seen before pregnancy, she should be told to cease topical retinoids. However, if she used topical retinoids until her pregnancy was confirmed at eight weeks

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she may consider a termination because of such warnings, and possibly, not fully understanding the differences between topical and oral preparations.

Regarding topical fluorouracil, it is of some concern that the authors cite drug company product information about malformations and miscarriage, but then fail to quote the subsequent sentence in the reference guide[1] which is far more important and says 'It is not known if there is a causative relationship between the topically applied drug and these outcomes'. Also, malformations seen following topical use (with approximately 6% systemic absorption) were completely different to those seen after systemic exposure, making a causal relationship even more tenuous. If drug information specialists have difficulties interpreting such nuances, how is a poor patient or busy GP supposed to deal with this data.

We all want what is best for pregnant women and their babies and this starts with sound evidence-based advice and counselling about medication risks and benefits, not a simplistic alphabet soup.

Editor, – The recent editorial by Debra Kennedy (Aust Prescr 2014;37:38-40) describes a longstanding and complex problem in medicines information. Unfortunately, Dr Kennedy's understanding of content found in the Australian Medicines Handbook (AMH) – that it 'essentially consists of the Australian Drug Evaluation Committee categorisation and the company product information' – is incorrect.

Great care and significant consideration of available evidence is taken in crafting the brief advice we provide. In the section on prescribing for pregnant women we say:

> Our advice is based on human data and clinical experience. Animal studies are not used as the sole sources of information upon which advice is based, as their interpretation with respect to human risk is not clear. Advice provided may not mirror the approved product information. Absence of information in AMH does not imply safety. Australian categories of safety, from the database Prescribing medicines in pregnancy, are included where they exist.

For nifedipine, the product information states 'Category C: nifedipine is contraindicated throughout pregnancy'. It then describes a range of potential fetal impacts on the basis of maternal hypotension, and adverse fetal effects seen in animal species. However, the AMH advises nifedipine is 'used to suppress preterm labour and for hypertension in pregnancy'. This reflects current evidence and practice, as nifedipine is the preferred tocolytic in Australia. The AMH also includes preterm labour as an accepted indication for use of nifedipine.

It is impossible to reduce complex information to a one-letter categorisation. The plan announced by the US Food and Drug Administration over five years ago, to eliminate the pregnancy categorisation, and replace it with drug-specific interpretations of available data, confirms this.

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Debra Kennedy, the author of the editorial, comments:

Thank you for pointing out my error in essentially lumping the AMH with other sources of information such as MIMS and the product information. I apologise if this caused any offence or confusion. I am the first to acknowledge the AMH as a valuable source of information regarding the use of medications in pregnancy. I did not intend to criticise its content.

I did, however, wish to point out that the AMH still includes the Australian Drug Evaluation Committee categorisation as well as some narrative and that therefore at times (in my opinion at least) it contains information that is somewhat internally contradictory. One example is hydroxychloroquine which is listed in the AMH as being indicated to treat 'rheumatoid arthritis (mild), discoid and systemic lupus erythematosus and prophylaxis and treatment of malaria if chloroquine is not available', but then goes on to say that it is 'safe to use for malaria; for other indications contact one of the pregnancy drug information centres; Australian category D'. I am not sure that this is either helpful or accurate. Why is the drug safer in pregnancy for one indication than another? The reality is that in Australia far more women will be using it for rheumatological conditions than for malaria. Furthermore, it is unclear why the drug is actually category D as there is no compelling evidence, to my knowledge, of it increasing the risk of birth defects. This would be a more valuable statement than any of the above.