

## Letters

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### Smoking cessation

Editor, – It was with considerable disappointment that I read J. Litt's contribution 'What's new in smoking cessation?' (Aust Prescr 2005;28:73–5). Nothing the author reviewed was new. The only truly new development in the field of smoking cessation has been the anti-nicotine vaccine. This did not seem to get a mention in the article at all. A lot of experimental research in animals has been published since 2002 and a review of current progress has recently been published.<sup>1</sup>

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1. Cerny T. Anti-nicotine vaccination: where are we? Recent Results Cancer Res 2005;166:167-75.

*Dr John Litt, the author of the article, comments:*

Nicotine is the main addictive agent in cigarettes.<sup>1</sup> A nicotine vaccine offers an additional therapeutic option to reduce the likelihood of relapse in smokers who have recently quit. Its role in assisting cessation or preventing the development of nicotine addiction remains speculative.<sup>2</sup>

Animal models have shown proof of concept.<sup>3</sup> Specifically, vaccination with a nicotine conjugate vaccine in mice produces antibodies that prevent nicotine crossing the blood-brain barrier. The vaccine also prevents the nicotine stimulation of dopamine release in the nucleus accumbens. This pathway is the postulated pleasure/reward pathway associated with various addictions, including nicotine. Blocking significant nicotine uptake in the brain reduces the rapid gratification effect and interrupts the subsequent reward provided by smoking. The process is not compromised by concomitant nicotine administration, suggesting that the vaccine may have a role in cessation.

The first phase I study was only published in July 2005.<sup>4</sup> After being immunised with a nicotine vaccine conjugated with bacteriophage Qb virus-like particles, 32 volunteers had significant increases in nicotine-specific IgM and IgG titres at 7 and 14 days respectively. Local reactions including erythema, local swelling and tenderness were common (88–100%) and a variable number (13–38%) experienced flu-like symptoms 2–12 hours post-injection.

A phase II trial is currently underway to assess vaccine efficacy. This and subsequent phase II studies will need to address a number of unknowns. For example, it is possible that the smoker may be able to alter their inhalation of nicotine and overcome the relative blockade of nicotine uptake into the brain.<sup>5</sup> How many boosters are required? What is the duration of immunity? What longer-term adverse effects are there? Most investigators agree that the anti-nicotine vaccine, if shown to be efficacious, will only provide an adjunct to counselling and other strategies, for example referral to an active callback program offered by state Quitlines.<sup>2,5</sup> A vaccine is unlikely to assist the patient in overcoming the habit of smoking or provide a coping strategy for dealing with negative emotions.

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### Upper gastrointestinal haemorrhage

Editor, – In the article 'Management of acute bleeding in the upper gastrointestinal tract' (Aust Prescr 2005;28:62–6), the authors say that an infusion of a high-dose proton pump inhibitor for 72 hours is recommended and they give the dosing recommendation for omeprazole.<sup>1</sup> Recently, AstraZeneca has discontinued the intravenous preparation of omeprazole, replacing it with esomeprazole. Consequently, we wish to comment on the choice of proton pump inhibitor now that omeprazole is unavailable.

Almost all clinical trials evaluating continuous infusion in acute gastrointestinal bleeding have used omeprazole. The efficacy of other proton pump inhibitors in equivalent doses is unproven. There are no published trials directly comparing, for example, intravenous omeprazole and pantoprazole for nonvariceal acute upper gastrointestinal bleeding. There is a study of healthy people, uninfected by *Helicobacter pylori*, which compared intravenous esomeprazole 40 mg with

pantoprazole 40 mg once daily. It showed that esomeprazole provides faster and more pronounced control of intragastric acidity.<sup>2</sup> We are unaware of any published studies on the use of continuous infusion of esomeprazole.

Esomeprazole is the S-enantiomer of omeprazole and has the same pharmacological activity.<sup>3</sup> The major difference between the enantiomers is in their pharmacokinetics. After equivalent doses, esomeprazole reaches higher plasma concentrations.<sup>4</sup> The manufacturer has provided unpublished data based on a study in healthy volunteers comparing the effects of various regimens of esomeprazole on maintaining intragastric pH > 4 and pH > 6. The results showed that intravenous esomeprazole 80 mg when given as an initial bolus dose over 30 minutes, followed by a continuous infusion of 8 mg/hr, maintained intragastric pH > 4 and pH > 6 for longer during a 24-hour period than other dosages.

Given the limited data that are available, we are recommending esomeprazole when continuous infusions are necessary, until further evidence becomes available. The dosage for esomeprazole should follow those suggested for continuous infusions of omeprazole, with an initial 80 mg dose given over 30 minutes, followed by continuous infusion of 8 mg/hr (at a concentration of 0.4 mg/mL) over 72 hours.<sup>5</sup>

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*Professor R.J. Fraser, one of the authors of the article, comments:*

As mentioned in our article, the current standard for pharmacological treatment for non-variceal upper gastrointestinal haemorrhage is intravenous omeprazole or equivalent. Omeprazole has been the proton pump inhibitor studied in the majority of published clinical trials, but a small number have involved other drugs.<sup>1</sup> Esomeprazole, which will soon replace omeprazole, obviously fulfils the criteria of equivalence, but it is unlikely to be the only drug to do so. Esomeprazole is an enantiomer, with theoretical benefits in terms of metabolism, but to date this has not been shown to provide significant overall benefits compared to racemic preparations.

Many clinicians believe the benefits in gastrointestinal haemorrhage result from a class effect, with the rise in intraluminal pH and resultant clot stability the key to improved outcome. The exact parameters that determine clot stability and the speed with which these need to be attained are unknown. The unpublished data reporting superior acid control in healthy volunteers are likely to have limited relevance to patient therapy. Although drug potency and the speed of acid suppression are clearly important, using these unpublished data to infer benefit in patient management is unjustified. More data are required in patients before making definite recommendations. For economic reasons, and in the absence of comparative randomised clinical trials in patients with gastrointestinal haemorrhage, clinicians frequently prescribe alternatives to omeprazole. Until such trials are done, the selection of proton pump inhibitor will continue to be a balance between cost, potential benefits and ease of administration in the face of incomplete evidence.

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## Biochemical tests in pregnancy

Editor, – In addition to the tests mentioned in the article 'Abnormal laboratory results: Biochemical tests in pregnancy' (*Aust Prescr* 2005;28:98-101), there are several other tests where the changes in the normal ranges during pregnancy are of clinical importance.

- Serum bicarbonate falls by approximately 4 mmol/L to compensate for the respiratory alkalosis which results from elevated progesterone concentrations stimulating respiratory drive.<sup>1</sup>
- Serum vitamin B<sub>12</sub> falls in 25% of pregnant women such that a value of greater than 100 pmol/L should be

regarded as normal for pregnancy. In the absence of folate deficiency serum homocysteine is of value in establishing true B<sub>12</sub> deficiency in pregnancy.<sup>2,3</sup>

- Erythrocyte sedimentation rate rises significantly (often up to 100 mm/hour).<sup>4</sup>
- White cell count rises due to neutrophil leucocytosis.<sup>5</sup>
- D-dimer becomes elevated in second and third trimesters.<sup>6</sup>
- Free protein S concentrations fall significantly.<sup>7</sup>
- Creatine kinase (MB subfraction) rises after vaginal delivery.<sup>8</sup>
- Serum troponin may be elevated in pre-eclampsia making diagnosis of myocardial ischaemia problematic if mothers develop pulmonary oedema.<sup>9</sup>
- Plasma renin activity and serum aldosterone rise masking detection of primary aldosteronism as a cause of pre-gestational hypertension in pregnancy.<sup>10</sup>

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*Dr H.A. Tran, author of the article, comments:*

Dr Morton's comments on other laboratory parameters that change during pregnancy are very much appreciated. The article aimed to highlight biochemical changes in common tests without being overly exhaustive. Generally speaking, pregnancy is a volume retentive, prothrombotic and nutritionally challenged state which results in all the corresponding changes described.

The hypervolaemic state is the result of an activated renin-angiotensin system with markedly elevated aldosterone concentrations and plasma renin activity. The normal physiological control of this system however remains intact, distinguishing it from primary hyperaldosteronism during pregnancy.<sup>1</sup>

The prothrombotic state is highlighted by the elevated d-dimer concentrations and reduced free protein S concentrations. The latter is the result of elevated protein binding capacity which is typical of pregnancy. Similarly, elevated transcobalamin and haptocorrin concentrations contribute to the reduction in cobalamin concentrations<sup>2</sup> although preferential fetal transfer during pregnancy also adds to the problem, particularly in vegans. It is probably more cost-effective to replenish B<sub>12</sub> storage empirically for the duration rather than relying on homocysteine concentrations to diagnose B<sub>12</sub> deficiency. Erythrocyte sedimentation rate, by way of physiological anaemia during pregnancy, is expected to be elevated but usually not to 100 mm/hour. The mean peak ranges from 50–70 mm/hour depending on the gestational age.<sup>3</sup> Thus, where it exceeds 100 mm/hour it is important that active inflammation or infection is excluded. Similarly, while white cell count can rise up to 15–16 × 10<sup>6</sup>/mL, the majority often do not exceed the non-pregnant reference range.<sup>4</sup>

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### Ciprofloxacin and fever

Editor, – Adverse drug reactions are a common problem in medical practice and can present in a variety of ways. Fever is not an uncommon manifestation and may confuse the prescriber.

We have recently seen three cases involving patients who were taking ciprofloxacin for febrile illnesses. While their conditions improved the patients remained febrile until they stopped the ciprofloxacin. We remind readers that fever is one of the more common adverse reactions reported with ciprofloxacin.

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### Dental dizziness

Editor, – I refer to the article 'Dealing with dizziness' (Aust Prescr 2005;28:94–7). I wish to recount a personal experience where, following dental treatment during which my head and neck were held in a rotated position for some time, I suffered an acute, but fortunately brief episode of severe dizziness and recall feeling 'queer' when given the all clear to sit up. Two days later I was confined to bed for 36 hours with an acute episode from which I recovered completely. Subsequent doppler studies revealed no evidence of compromised cerebral circulation. Is it possible that unusual posturing of one's head during dental therapy could be another cause of an acute episode of dizziness?

Judy Rice  
Pharmacist  
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*Dr Mark Paine, the author of the article, comments:*

The scenario is very suggestive of benign paroxysmal positional vertigo. The positioning of the patient during the dental treatment is very similar to the Hallpike positioning manoeuvre. While a bout of positional vertigo is usually brief, there may be after-effects causing persisting low grade dizziness which may last hours to days. To be certain about this diagnosis, it is essential to examine the patient during the episode.

*Dr M. McCullough, Australian Dental Association, comments:*

An acute feeling of dizziness following prolonged dental treatment is not uncommon in dental practice. Sudden changes in blood pressure following postural changes after prolonged periods in a supine dental chair may be responsible. Usually, if patient and dentist are aware of this possibility, then treatment procedures can be kept to shorter duration, with rest breaks during the procedure.

Postural hypotension is unlikely to explain the episode occurring two days after the dental procedure. Possible explanations to consider include tooth extraction and subsequent haemorrhage with breakdown of haemostasis, infection and acute dental pain causing decreased nutrition or hydration.

### 'Statins' and muscle symptoms

Editor, – With 12 years of 'statins' under my personal belt I feel able to comment on the medicinal mishap 'Statins and muscle symptoms' (Aust Prescr 2005;28:102), particularly the checklist of muscle symptoms. My observations over many years since I first recognised the connection between my muscle pains and simvastatin, and briefly atorvastatin, lead me to assert that the pain:

- is severe enough to wake you up
- tends to be nocturnal, within 2–8 hours of the last dose, unless the statin is taken in the morning
- is quickly and surprisingly easily relieved by a few contractions of the muscle concerned, or a walk to the bathroom – the ensuite may not be far enough
- recurs in the same area of muscle, which is tender to touch and also on contraction
- is never symmetrical – my right vastus lateralis was originally involved, and lately my left deltoid muscle.

Earlier I could control the symptoms by leaving out my daily dose of 10 mg on two days per week, but relief (that is unbroken sleep) sometimes took 24 hours. I tested this response perhaps dozens of times.

The insouciance of an overseas trip three months ago led me to taking a tablet **every** day. The result was persistent pain and weakness in the same muscle, and ultimately wasting, to the point where I was unable to step up with the right leg – a drastic disability in Europe.

After stopping the drug for two months, my thigh is nearly back to normal, but I can still feel the affected area. My lipids are not optimal now, but creatine kinase seems unaffected.

There seems little prospect of these adverse effects being reported to the Adverse Drug Reactions Advisory Committee because both my general practitioner and cardiologist attributed them (not so definitely of late) to my old age. I graduated in medicine 54 years ago. Having experienced both, I find old age much easier to take, so far, than the adverse effects I have experienced with the statins.

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