

Hydrofluoric acid burns from a household rust remover

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TO THE EDITOR: The report by Mangion et al¹ draws attention to a serious risk in the environment. The general public has been increasingly protected against the risk of harm from domestic products by a combination of legal liability actions and government regulation. Thus, the continuing availability to the general public of hydrofluoric acid (HF) in concentrations that are hazardous is something of an anachronism.

While we applaud Mangion and colleagues for raising the issue of HF burns, we feel that their article is deficient in failing to mention a number of important points.

- Topical calcium gluconate has been shown to be more effective in treating HF burns if the preparation contains dimethyl sulfoxide (DMSO).²

- There is a great risk of blindness with ocular exposure to HF.

- Slow local injection with 10% calcium gluconate using fine needles, titrating its effect against the patient's pain, is a well described technique. This is another treatment option that could have been tried.

- Nail removal, described by Mangion et al as an "extreme measure", is, unfortunately, often required. It is less likely to be required with the application of DMSO/calcium gluconate solution and retrograde ischaemic intravenous injection of calcium.

- Local excision of contaminated tissue may be required after exposure to concentrated solutions.

- Management should be a team effort from the first moment, involving an intensivist/toxicologist and surgeon, as burns surgeons are trained in the care of HF exposure, and surgery is often needed.

The availability, packaging, and labelling of preparations containing HF have recently been changed. Since 1 December 2001 it has no longer been possible for the general public to purchase any HF preparation stronger than 1%. All preparations now carry prominent labelling drawing attention to the risk of blindness if even dilute solutions of HF get into the eyes. Containers are now less easy to open by children.

These changes have been introduced by the National Drugs and Poisoning Committee of the Therapeutic Goods Administration as a result of an independent review

and lobbying by the Australian and New Zealand Burn Association (ANZBA).

The ANZBA guidelines for referral to a specialised burns unit include chemical burns. The peculiar challenge posed by HF burns emphasises the need for the guidelines to be more widely disseminated. Currently, the New South Wales Department of Health has adopted the guidelines, so this policy is official throughout New South Wales.

1. Mangion SM, Beulke SH, Braitberg G. Hydrofluoric acid burn from a household remover. *Med J Aust* 2001; 175: 270-271.

2. Seyb ST, Noordhoek L, Botens S, Mani MM. A study to determine the efficacy of treatments for hydrofluoric acid burns. *J Burn Care Rehabil* 1995; 16(3 Pt 1): 253-257. □

Renal protection by angiotensin II receptor antagonists in patients with type 2 diabetes

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TO THE EDITOR: A recent editorial in the Journal attempted to define a role for angiotensin II receptor (AII) antagonists in patients with type 2 diabetes.¹ This was in the light of recent trial evidence that these agents reduce progression to renal failure in patients with type 2 diabetes and diabetic renal disease. Unfortunately, the guidelines provided were somewhat confusing and fragmented. I believe that a simpler treatment guide can be constructed, particularly when it is emphasised that the aim in diabetes is to use agents that prevent not only renal failure but also cardiovascular events.

Substantial evidence already supports a role for the angiotensin-converting enzyme (ACE) inhibitor ramipril in treatment of diabetes. The HOPE study included 3577 people with diabetes and another risk factor for cardiovascular disease who were randomised to either placebo or ramipril

(10 mg) for 4.5 years.² This group had a mean baseline blood pressure of 142/80 mmHg and no clinical proteinuria. Ramipril lowered the risk of the combined primary outcome of myocardial infarction, stroke and cardiovascular death by 25% ($P \leq 0.001$), and this effect was independent of blood-pressure lowering. Furthermore, ramipril reduced progression to overt nephropathy by 22%, with a reduction evident in patients with or without proteinuria.²

This protective effect of ramipril on renal function is consistent with previous evidence that ACE inhibitors slow progression of chronic renal failure in diabetes,^{3,4} and that ramipril slows progression of chronic renal failure in non-diabetic nephropathy.⁵

Whether other ACE inhibitors have the same effect as ramipril on cardiovascular events, and what doses obtain such an effect, remains speculative. Similarly, while there is now evidence that AII antagonists also have renal-protective effects, there is no definitive evidence that they protect against cardiovascular events.

In view of this, and in the absence of comparative trials, ramipril (and not other ACE inhibitors or AII antagonists) is currently the first choice for treatment for diabetic patients with hypertension, with normotension and microalbuminuria, or with hypertension and micro- or macroalbuminuria. As most patients with diabetes and hypertension require multiple agents to achieve a target blood pressure less than 130/80 mmHg, additional therapy with a β -blocker, diuretic or calcium-channel blocker is often necessary.

The significance of the newly available trial data is that AII antagonists provide an alternative to ramipril for reducing progression to chronic renal failure in patients with diabetic nephropathy who cannot tolerate ACE inhibitors because of the side effect of cough.

1. Jerums G, Cooper ME, Gilbert RE, Atkins RC. Renal protection by angiotensin II receptor antagonists in patients with type 2 diabetes [editorial]. *Med J Aust* 2001; 175: 397-399.

Correspondents

Letters must be no longer than 400 words and must include a word count. All letters are subject to editing. Proofs will not normally be supplied. There should be no more than 4 authors per letter. Each author should provide current qualifications and position. Contact telephone and facsimile numbers should be supplied. Letters from a single author may be submitted by email (editorial@ampco.com.au), but must include full details of postal address and telephone number. There should be no more than 5 references. The reference list should not include anything that has not been published or accepted for publication. Reference details must be complete, including: names and initials for up to 4 authors, or 3 authors, et al. if there are more than 4; places and dates for conferences and publishers, places and year of publication for their proceedings; publishers, places, year of publication and page numbers for monographs; volume numbers and page numbers for journal articles.

- Heart Outcomes Prevention Evaluation (HOPE) Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy [published correction appears in *Lancet* 2000; 356: 860]. *Lancet* 2000; 355: 253-259.
- Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993; 118: 577-581.
- Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. *Arch Intern Med* 1996; 156: 286-289.
- Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; 354: 359-364. □

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IN REPLY: Peverill raises the question of how to integrate the new data on renal protection by angiotensin II receptor (AIIR) antagonists with existing data on cardiovascular protection by angiotensin-converting enzyme (ACE) inhibitors in patients with type 2 diabetes. An AIIR antagonist would be favoured for renal protection for a diabetic patient with hypertension and evidence of early or overt nephropathy. With regard to patients with microalbuminuria, the HOPE and MICRO-HOPE studies showed that therapy with the ACE inhibitor ramipril (10 mg/day) was associated with a 24% relative risk reduction for the development of overt nephropathy over 4.5 years.¹ In contrast, treatment of similar patients with the AIIR antagonist irbesartan (300 mg/day) for 2.6 years resulted in a 70% risk reduction for the development of overt nephropathy.² Use of an AIIR antagonist in patients with overt nephropathy has also been shown to slow progression to end-stage renal failure.^{3,4} As the HOPE and MICRO-HOPE studies specifically excluded such patients, evidence supporting use of an ACE inhibitor in this context is lacking.

An ACE inhibitor could be used if a diabetic patient has microalbuminuria and a history of coronary heart disease or additional risk factors for cardiovascular disease, especially if normotensive. However, almost all patients with microalbuminuria require antihypertensive therapy as well as therapy to protect target organs. The relative importance of blood-pressure-lowering versus non-lowering effects of antihypertensive therapy on reducing risk of cardiovascular disease remains uncertain.⁵ Furthermore, a recent meta-analysis of cardiovascular protection in 62 605 patients

with hypertension (including the HOPE and United Kingdom Prospective Diabetes studies) did not find that ACE inhibitors affected cardiovascular prognosis beyond their antihypertensive effects.⁶

Finally, it is important to note that neither ACE inhibitors nor AIIR antagonists provide total protection from cardiovascular and renal events, and that further improvements are needed for both microvascular and macrovascular protection in patients with type 2 diabetes.

- Heart Outcomes Prevention Evaluation (HOPE) Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355: 253-259.
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- Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345: 851-860.
- Brenner BM, Cooper ME, De Zeeuw D, et al for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861-869.
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- Staessen JA, J-G Wang, Lutgarde T. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; 358: 1305-1314. □

Pharmacological treatment of cognitive deficits in Alzheimer's disease

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TO THE EDITOR: The review by Brodaty and colleagues¹ on drug treatment of Alzheimer's disease provides a good, concise and balanced overview. However, Pfizer takes issue with some of the referenced safety data.

In Box 3 of that article (Profiles of cholinesterase inhibitors), in reference to adverse effects of donepezil (Aricept, Pfizer), it is stated that "At 10 mg/day, nausea (17% of patients), diarrhoea (17%) and vomiting (10%) may occur.⁴⁹" Reference 49 at this point appears to be an incorrect citation.

The figures of 17%, 17% and 10% for nausea, diarrhoea and vomiting, respectively, appear to have been taken from an article by Rogers and Friedhoff.² It is important to note that this was a non-comparative, open-label extension study, and these incidences of gastrointestinal adverse events are inconsistent with data presented in the Australian Product Information for donepezil,³ which quote rates of

nausea, diarrhoea and vomiting of 11%, 10% and 5%, respectively. These incidences are derived from a patient cohort of 1102 patients who participated in appropriately designed comparative (active and placebo) pre-registration studies of donepezil. These data have recently been confirmed in a one-year, randomised, placebo-controlled study of donepezil in patients with mild to moderate Alzheimer's disease.⁴ Incidences of 11.3%, 7.0% and less than 5% for nausea, diarrhoea and vomiting, respectively, are quoted in that study.

We contend that, while the citation referenced by Brodaty et al was incorrect, the figures quoted for the gastrointestinal safety incidences for donepezil are also inconsistent with the Product Information and current published data.

- Brodaty H, Ames D, Boundy KL, et al. Pharmacological treatment of cognitive deficits in Alzheimer's disease [review]. *Med J Aust* 2001; 175: 324-329.
- Rogers S, Friedhoff L. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicentre open label extension study. *Eur Neuropsychopharmacol* 1998; 8: 67-75.
- Australian-approved Product Information for Donepezil. Sydney: Pfizer Pty Limited, 10 December 2001.
- Winblad B, Engedal K, Soinen H, et al and the Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; 57: 489-495. □

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IN REPLY: We thank Lam for pointing out an error in the referencing in Box 3 of our article¹ regarding the figures for adverse events for donepezil. The correct reference was number 48 in our list, not 49, and was to Rogers, Farlow, Doody et al,² not to Rogers and Friedhoff,³ as suggested by Lam. The other references in Box 3 were given as 20, 21, 23 and 48, but should have been listed as 19, 20, 21 and 47, respectively.

Secondly, issue is taken with the rates of 17%, 17% and 10% for nausea, diarrhoea and vomiting, respectively, in people taking donepezil. We agree with the overall tenor of this letter that rates of side effects are generally lower in everyday practice.

The figures we quoted for adverse events are higher than the 11%, 10% and 5% cited