

EVIDENCE-BASED MEDICINE: A HISTORICAL AND INTERNATIONAL REVIEW

Sir, Like Professor Woolf,¹ I would utilise even the highest level of evidence, namely, the randomised control trial, as an opportunity to search for gaps, especially those which can be evaluated by recourse to basic science. A case in point was the RALES trial, in which heart failure patients on diuretics and angiotensin converting enzyme (ACE) inhibitors experienced an additional survival benefit when co-prescribed spironolactone in a dose of 25–50 mg/d.² Nowhere in the list of adverse events (Table 4) was there any mention of pre-renal uraemia. This is notwithstanding that among the consequences of ‘triple blockade’ of sodium reabsorption at sites that included the proximal renal tubule (through the mediation of ACE blockade),³ the ascending portion of the loop of Henle (mediated by loop diuretics) and the distal nephron (mediated by spironolactone), is a powerful augmentation of diuresis beyond that achievable with blockade at only two sites.^{4,5} This may result in pre-renal uraemia, even in spironolactone doses of 25–50 mg/d.^{4,5} In the Wistar rat model of heart failure, even co-prescription of only spironolactone and an ACE inhibitor powerfully augments the natriuresis resulting from the use of either agent on its own.³ On the basis of these observations,^{3,5} the episodes of severe pre-renal uraemia (with or without co-existing diarrhoea),^{6,7} which have been reported in heart failure patients receiving ‘triple therapy’ with ACE blockade, loop diuretics, and spironolactone could be attributable, at least in part, to excessive augmentation of diuresis. Recourse to first principles of basic sciences can, therefore, fill the gaps not covered by clinical trial evidence.

O.M.P. JOLOBE

NHS Consultant, Tameside General Hospital, Ashton-under-Lyne

REFERENCES

- 1 Woolf S. Evidence-based medicine: a historical and international overview. *Proc R Coll Physicians Edinb* 2001; **319**:39–41.
- 2 Pitt B, Zannad F, Remme WJ *et al.* for the RALES Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341**:709–17.
- 3 Bauersachs J, Fraccarollo D, Ertl G *et al.* Striking increase of natriuresis by low-dose spironolactone in congestive heart failure only in combination with ACE inhibition. Mechanistic evidence in support of RALES. *Circulation* 2000; **102**:2325–8.
- 4 Ikram H, Webster MWI, Nicholls MG *et al.* Combined spironolactone and converting-enzyme inhibitor therapy for refractory heart failure. *Aust N Z J Med* 1986; **16**:61–3.
- 5 Jolobe OMP. Efficacy of low-dose captopril in addition to furosemide and spironolactone in patients with decompensated liver disease during blunted diuresis (letter). *J Hepatol* 1993; **19**:321–2.
- 6 Berry C and McMurray JJV. Serious adverse events experienced by patients with chronic heart failure taking spironolactone. *Heart* 2001; **85**:e8.
- 7 Schepkens H, Vanholder R, Billiouw J-M *et al.* Life-threatening hyperkalaemia during combined therapy with angiotensin-converting-enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med* 2001; **110**:438–41.

LETTER FROM ZIMBABWE

Sir, I would like to thank the College for continuing to send me copies of the *Proceedings*. I think it must have been the late Professor Petrie who allowed me this ‘honorary’ subscription, for which I am extremely grateful, in our troubled times in Zimbabwe. The tribute to Professor Petrie was very moving and it was good that he should be remembered by the SIGN publications which he helped to institute. The *Proceedings* helps me to keep up-to-date in my present job as Medical Liaison Officer, at one of the few functioning health facilities. The fancy title is merely a euphemism for clinical audit and listening to the two-way complaints between doctors and the clinic. I also try to point to useful clinical guidelines and interesting recent articles in a monthly newsletter to the doctors. Again, many thanks.

J.E.P. THOMAS

Medical Liaison Officer, The Avenues Clinic, Zimbabwe

Letters are welcome providing they do not exceed 300 words in length. The Editor reserves the right to edit correspondence.