Diabetologia

Authors' reply

To the Editor: We agree with R. Biswas et al. that our recent study did not find the combination of aminoguanidine and perindopril to afford total renoprotection or to be superior to monotherapy in terms of all renal parameters studied [1]. We consider albuminuria to be a major functional marker of diabetic nephropathy, and demonstrated in our recent study that the combination was superior to individual agents in attenuating the progressive increase in albumin excretion rate in diabetic spontaneously hypertensive rats [1]. However, other markers of renal injury such as renal TGFβ expression and glomerular and tubulointerstitial injury, although reduced by both forms of monotherapy, were not further decreased by combination therapy.

We agree that perindopril and indeed other agents that interrupt the renin–angiotensin system, such as AII antagonist, are inhibitors of AGE formation, as initially reported in in vitro studies [2]. Indeed, our group has reported in vivo AGE inhibition with the ACE inhibitor, ramipril [3] and more recently in diabetic spontaneously hypertensive rats with perindopril [1]. This in vivo inhibition has now been confirmed in another model of diabetic nephropathy using the AII antagonist, irbesartan [4]. Interestingly, hydralazine was also reported to decrease AGE formation [4], and previous studies suggest that dihydropyridine calcium channel blockers do not inhibit AGE formation [2].

Our own group has, over the last 10 to 15 years, investigated a number of antihypertensive agents in diabetic spontaneously hypertensive rats, and demonstrated antiproteinuric effects with the combination of hydralazine and metoprolol [5] but not with the calcium channel blockers, amlodipine [6] or lacidipine [7]. Although, at the time, we did not appreciate that some of these antihypertensive agents were AGE inhibitors, it is interesting to speculate that one of the potential explanations for the renoprotection that is conferred by some but not other antihypertensive agents may in fact be related to the specific drug's ability to modulate the glycation pathway.

We acknowledge that one must be cautious in interpreting the findings of rodent studies when placed in a human context. Indeed, the dose of agents such as ACE inhibitors is likely to be an important factor in determining the degree of renoprotection. However, in this study [1], we wanted to compare equivalent doses of ACE inhibition, with or without additional inhibition of AGE formation with aminoguanidine, and were able to show that for the same blood pressure reduction, the combination was more potent at reducing albumin excretion rate. However, as alluded to by Biswas et al., no such reduction in the relatively mild renal structural abnormalities could be demonstrated.

B. J. Davis, T. J. Allen, M. E. Cooper
Diabetic Complications Group, Baker Heart Research Institute, Prahran, Melbourne, Australia

B. J. Davis
Department of Diabetes, Endocrinology and Internal Medicine, Unit for Metabolic Medicine, 5th floor Thomas Guy House, King's College London, Guy's Hospital, London, UK

References

1. Davis BJ, Forbes JM, Thomas MC et al. (2004) Superior renoprotective effects of combination therapy with ACE and AGE inhibition in the diabetic spontaneously hypertensive rat. Diabetologia 47:89–97
2. Miyata T, Ypersele de Strihou C van, Ueda Y et al. (2002) Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: biochemical mechanisms. J Am Soc Nephrol 13:2478–2487
3. Forbes JM, Cooper ME, Thallas V et al. (2002) Reduction of the accumulation of advanced glycation end products by ACE inhibition in experimental diabetic nephropathy. Diabetes 51:3274–3282
4. Nangaku M, Miyata T, Sada T et al. (2003) Anti-hypertensive agents inhibit in vivo the formation of advanced glycation end products and improve renal damage in a type 2 diabetic nephropathy rat model. J Am Soc Nephrol 14:1212–1222
5. Cooper ME, Allen TJ, O'Brien RC et al. (1990) Nephropathy in model combining genetic hypertension with experimental diabetes. Enalapril versus hydralazine and metoprolol therapy. Diabetes 39:1575–1579
6. Davis BJ, Cao Z, Gasparo M de et al. (2003) Disparate effects of angiotensin II antagonists and calcium channel blockers on albuminuria in experimental diabetes and hypertension: potential role of nephrin. J Hypertens 21:209–216
7. Rumble JR, Doyle AE, Cooper ME (1995) Comparison of effects of ACE inhibition with calcium channel blockade on renal disease in a model combining genetic hypertension and diabetes. Am J Hypertens 8:53–57

B. J. Davis (✉)
Department of Diabetes, Endocrinology and Internal Medicine, Unit for Metabolic Medicine, 5th floor Thomas Guy House, King's College London, Guy's Hospital, London, SE1 9RT, UK
E-mail: Belinda.davis@kcl.ac.uk
Tel.: +44-20-71881935, Fax: +44-20-71880146

DOI 10.1007/s00125-004-1470-z
Received: 16 June 2004 / Accepted: 18 June 2004
Published online: 23 July 2004