Optimal dosing of renin–angiotensin–aldosterone system blockers for renal protection: a solved issue?

G. D. Laverman · S. J. L. Bakker · G. J. Navis

Received: 13 February 2009 / Accepted: 23 February 2009 / Published online: 18 March 2009
© The Author(s) 2009. This article is published with open access at Springerlink.com

Abbreviations

ARB Angiotensin receptor blocker

RAAS Renin–angiotensin–aldosterone system

To the Editor: Schjoedt et al. [1] convincingly demonstrated that at group level a daily dose of 40 mg of the ACE inhibitor lisinopril provides maximum reduction of proteinuria in patients with type 1 diabetes and nephropathy. The importance of the issue of dose is widely appreciated, but it is surprising how little effort has been made to find the optimal dose of a single agent, while numerous studies have been performed worldwide to test the additional anti-proteinuric benefit of dual renin–angiotensin–aldosterone system (RAAS) blockade (angiotensin converting enzyme inhibitor plus angiotensin receptor blocker [ARB]). The authors must therefore be acknowledged for their contribution.

Does, however, a maximal effect at a dose of 40 mg in a group imply that 40 mg has a maximal effect in all individual patients? We would suggest not. In our experience in non-diabetic patients with overt proteinuria, the dose of lisinopril required for maximal anti-proteinuric effect varies between patients [2]. Schjoedt et al. also mention that their patients had considerably impaired renal function. Considering the renal clearance of lisinopril, circulating plasma levels of lisinopril were presumably high. Thus it is possible that in patients with better preserved glomerular filtration rate, higher daily doses of lisinopril would be required for comparable plasma levels

of the drug and efficacy. In addition, other patient factors such as type of renal lesion or genetic make-up could influence inter-individual differences in drug response. Therefore, the evidence so far does not exclude the possibility that daily doses of lisinopril higher than 40 mg may be required in some patients.

Nevertheless, it would be unrealistic to claim that high-dose RAAS blockade alone has the potential to completely reverse proteinuria in the majority of patients, not even when given in combination with ARB. The limits may be set not only by efficacy, but also by side effects, as illustrated in patients with non-diabetic proteinuria on a high dose (300 mg) of the ARB irbesartan [3]. When lisinopril was added in incremental doses up to 40 mg, adverse events (hyperkalaemia, cough, dizziness) occurred in most patients.

Since the results of the Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting-enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial have been seriously questioned [4], and with the recent results on renal endpoints of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) in mind [5], the issue of whether dual RAAS blockade leads to improved long-term renal protection should be addressed in a new randomised study, specifically designed for that purpose. We would strongly favour a design in which dual blockade consists of a combination of the optimal anti-proteinuric doses in the individual patient. Until such data are available, we propose an individualised approach, with titration of a single drug based on the effect on proteinuria and on blood pressure, and the extent of side effects. If necessary, a second drug could be added and again titrated, with careful monitoring of side effects being essential.

G. D. Laverman (✉) · S. J. L. Bakker · G. J. Navis
Department of Internal Medicine,
University Medical Center Groningen,
Groningen, the Netherlands
e-mail: g.d.laverman@int.umcg.nl

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

- Schjoedt KJ, Astrup AS, Persson F et al (2009) Optimal dose of lisinopril for renoprotection in type 1 diabetic patients with diabetic nephropathy: a randomised crossover trial. *Diabetologia* 52: 46–49
- Laverman GD, Navis G, Henning RH, De Jong PE, de Zeeuw D (2002) Dual renin-angiotensin system blockade at optimal doses for proteinuria. *Kidney Int* 62:1020–1025
- Vogt L, Navis G, de Zeeuw D (2005) Individual titration for maximal blockade of the renin-angiotensin system in proteinuric patients: a feasible strategy? *J Am Soc Nephrol* 16(Suppl 1):S53–S57
- Kunz R, Wolbers M, Glass T, Mann JF (2008) The COOPERATE trial: a letter of concern. *Lancet* 371:1575–1576
- Mann JF, Schmieder RE, McQueen M et al (2008) Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 372:547–553