Editorial

Angiotensin-Converting Enzyme Inhibition and Renovascular Disease

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Over the last decade the benefits of inhibition of the renin-angiotensin system in treatment of both hypertension and congestive cardiac failure have become well established. Initial anxieties that captopril therapy on occasion resulted in leukopenia or in proteinuria associated with membranous nephropathy have largely receded as, with the lower doses now employed, such side effects are very rare [1]. Of more concern was the early observation that when renal arterial stenosis was present, angiotensin-converting enzyme inhibitors could produce a dramatic reduction in glomerular filtration rate, severe enough to require support by renal dialysis [2]. This phenomenon has been widely confirmed, and may occur either when bilateral renal artery stenosis is present [3] or when there is arterial stenosis of a single functioning kidney [3], as for example a renal allograft [4]. In most, although not all, cases the acute deterioration in renal function has been fully reversible on withdrawal of the converting enzyme inhibitor [2-4].

The reasons for this functional deterioration have been clarified by animal studies. When renal perfusion is reduced, glomerular filtration rate is maintained by enhanced renin release which augments intra-renal angiotensin II formation, thereby increasing efferent arteriolar tone [5]. Inhibition of angiotensin-converting enzyme, by blocking angiotensin II formation, causes efferent arteriolar vasodilatation. This normally leads to an increase in renal plasma flow, with little change in glomerular filtration rate. However, if renal perfusion is limited by fixed stenoses of the renal arteries or arterioles, renal plasma flow cannot increase to compensate for loss of efferent arteriolar tone, and hence glomerular filtration falls.

These explanations are attractive, and are supported by studies in animals [6] and clinical observations [2, 3] which showed that renal function remained unchanged when blood pressure was lowered to an equivalent degree by therapy not including a converting enzyme inhibitor. However, in patients with severe bilateral renal artery stenoses of 70–95 per cent acute lowering of blood pressure with nitroprusside did reduce glomerular filtration by 50 per cent or more [7], confirming that non-specific loss of renal perfusion pressure is important when advanced renal vascular disease is present.

Kalra et al. have now carried out a retrospective study of 530 consecutive patients presenting acutely with uraemia to a Regional Renal Unit, and have implicated renovascular disease in 85 (16 per cent) of these. In 21 cases, uraemia was specifically attributed to ACE inhibitor therapy. A parallel survey of 400 consecutive patients referred to a specialist hypertension clinic suggested that 14.5 per cent had concomitant renovascular disease, although a causal relationship with blood pressure elevation was not proven [8]. These observations are of interest, since they support current perceptions that renovascular disease...
may be more common than hitherto documented as a cause of both hypertension and renal impairment. To some extent, this apparent increase may be due to both a growth in referral of elderly patients in whom atherosclerosis is more likely to be a dominant factor, and to improved non-invasive techniques for diagnosing renovascular disease, such as Doppler ultrasound scanning and radio-nuclide imaging.

Kalra et al. also draw attention to subgroups of patients who do not show the well-described acute but reversible deterioration in renal function in association with angiographically demonstrable stenosis. In some patients with glomerulonephritis, function improved with withdrawal of the inhibitors, despite the demonstration of normal renal arteries, illustrating that these drugs are equally capable of causing renal functional impairment when there is presumed microvascular narrowing, rather than macroscopic disease.

Uncomplicated, functional renal impairment induced by angiotensin-converting enzyme inhibitors is rapid in onset, with increases in serum urea and creatinine being evident within 2-3 days, and recovery is equally rapid, being complete in one to two weeks [3, 4]. It is disturbing, therefore, that five patients studied by Kalra et al. had irreversible renal failure, considered to be due to arterial occlusion in association with administration of these drugs. Furthermore, in cases where uraemia was reversible, this took 4-6 weeks after drug withdrawal. These observations highlight more serious potential hazards of angiotensin-converting enzyme inhibition, which may be due to their ability to cause rapid and profound initial falls in blood pressure [9]. These occur especially when the renin–angiotensin system is activated, as with volume depletion or diuretic use. Sudden hypotension superimposed on a severely atheromatous renal arterial supply may lead to irreversible intra-renal vascular thrombosis. Delayed improvement in function suggests that complications such as partial thrombotic occlusion or acute tubular necrosis occurred in association with severe hypotension.

What conclusions may be drawn from these experiences? First, a high index of suspicion for renovascular disease is required, especially in the elderly who have recent onset hypertension and associated renal impairment, or when there are symptoms such as claudication or angina suggesting widespread atheromatous disease. Diagnostic confirmation of functionally significant renal arterial stenosis remains difficult; the ultimate proof is retrospective, requiring clear-cut improvement in blood pressure or renal function with correction of the stenosis. A combination of DTPA and hippurate renography performed before and after a test dose of converting enzyme inhibitor appears the most rewarding screening test at present. In experienced centres, 100 per cent specificity has been reported [10]. Second, the introduction of angiotensin-converting enzyme inhibitors must always be done carefully. Hypovolaemia should be excluded, and ideally diuretics should be temporarily withdrawn to minimize the risk of excessive first-dose hypotension and its potential complications. If in any doubt, blood pressure response should be monitored for 1–2 hours after the initial dose.

Lastly, plasma electrolytes, urea and creatinine should be measured within a week of commencing inhibitor therapy. In this way, any acute deterioration in renal function will be readily detected, and should be fully reversible. It is then essential to investigate such patients further for occult renovascular disease which may be amenable to angioplasty or reconstructive surgery.

References


