Impact of renin angiotensin system blockade on night to day blood pressure ratio in diabetic nephropathy

Sir,

Elevated systemic blood pressure is a risk factor for progression of diabetic nephropathy. Ambulatory blood pressure measurements offer additional risk stratification compared to office blood pressure in patients with hypertension [1]. In addition, an abnormal diurnal blood pressure pattern characterized by an elevated night to day ratio is found more commonly in diabetic patients and, as reviewed by Miller et al. [2], is associated with poor renal outcome. The renin angiotensin system (RAS) is involved in both initiation and progression of diabetic nephropathy and blocking this system with ACE-inhibitors (ACE-I) and/or angiotensin II receptor blockers (ARBs) improves kidney survival and prognosis. Miller et al. [2] reported that treatment with enalapril (0.1 mg/kg BID) corrects the abnormally high night to day blood pressure ratio in 10 uncomplicated adolescents, and this could contribute to the beneficial renoprotective effects of RAS blockade. In this letter, we further investigate whether RAS blockade corrects an abnormal 24 h blood pressure pattern by presenting data on the short-term effects of single and dual blockade of the RAS on a 24 h blood pressure profile and a night to day blood pressure ratio in type 1 diabetic patients with diabetic nephropathy. Our data are a post-hoc analysis of three earlier studies [3–5]. As described previously [3], we performed a randomized, double blind, cross-over trial, in which 18 patients received 8 weeks of placebo, benazepril 20 mg once daily, valsartan 80 mg once daily and a combination of benazepril 20 mg and valsartan 80 mg once daily in random order [3]. The main findings were: (1) mono-therapy with ACE-I or ARBs treatment was equally effective with regard to antialbuminuric and antihypertensive effects; (2) dual blockade of the RAS caused a further reduction in albuminuria of 43% and 7/6 mmHg in 24 h blood pressure compared with both mono-therapies; (3) night to day ratio of 24 h blood pressure on each treatment is shown in Table 1. A post-hoc power calculation estimated a power in 0.80 to detect a difference of 0.05 in night to day ratio with a significance level of 0.05.

In agreement, when looking at the fraction of patients with night to day blood pressure ratio above the median on placebo treatment (>0.91), we found no changes in the night to day ratio on RAS blockade. Furthermore, in two other studies demonstrating that dual blockade of the RAS lowered albuminuria 25–37%, reduced 24 h blood pressure 8/4–5 mmHg and raised plasma renin compared with ACE-I alone in type 1 diabetic patients with nephropathy, we found no changes in the night to day blood pressure ratio (Table 1) [4,5]. Since, no placebo treatments were included, no data of the effects of single agent blockade of the RAS on blood pressure profile are available in these latter studies. The discrepancy between treatment effects on night to day blood pressure ratio in our complicated diabetic patients and the uncomplicated patients included in the study by Miller et al. [2] may well reflect the fact that the causes of abnormalities in blood pressure variation are different, leading to different degrees of reversibility.

In conclusion, our short term data indicates that commonly used ACE-I and ARBs, given once daily in the morning, reduce both night and day blood pressure, but do not influence the night to day ratio, in type 1 diabetic patients with diabetic nephropathy. Specific beneficial effects of RAS blockade are likely to involve local renal effects, and seem unrelated to an impact on 24 h blood pressure profile. However, a change in timing of RAS blockade to night time dosing is worth investigating.

Conflict of interest statement. P.K.J has received a lecture fee from Sanofi-Avensis. H.H.P. has been a consultant for Sanofi-Avensis, Merck, Pfizer, Novartis, Amgen and has received a grant from Sanofi-Avenis and Merck and lecture fees from the above mentioned pharmaceutical companies.

Table 1. Night to day ratio of 24 h blood pressure in type 1 diabetic patients with diabetic nephropathy—relation to RAS blockade

<table>
<thead>
<tr>
<th>Study, n</th>
<th>Placebo</th>
<th>ACE-I</th>
<th>ARB</th>
<th>Dual blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, n = 18 (3)</td>
<td>BP (mmHg)</td>
<td>144/79</td>
<td>129/73</td>
<td>129/73</td>
</tr>
<tr>
<td></td>
<td>Ratio systolic BP (night/day)</td>
<td>0.91 (0.76–1.04)</td>
<td>0.91 (0.68–1.00)</td>
<td>0.90 (0.76–1.06)</td>
</tr>
<tr>
<td></td>
<td>Ratio diastolic BP (night/day)</td>
<td>0.88 (0.75–1.00)</td>
<td>0.93 (0.73–1.05)</td>
<td>0.92 (0.70–1.03)</td>
</tr>
<tr>
<td>2, n = 19 (4)</td>
<td>BP (mmHg)</td>
<td>138/75</td>
<td>130/70</td>
<td>129/73</td>
</tr>
<tr>
<td></td>
<td>Ratio systolic BP (night/day)</td>
<td>0.93 (0.76–1.04)</td>
<td>0.92 (0.78–1.06)</td>
<td>0.92 (0.70–1.03)</td>
</tr>
<tr>
<td></td>
<td>Ratio diastolic BP (night/day)</td>
<td>131/74</td>
<td>123/70</td>
<td>122/70</td>
</tr>
<tr>
<td>3, n = 24 (5)</td>
<td>BP (mmHg)</td>
<td>130/70</td>
<td>123/70</td>
<td>122/70</td>
</tr>
<tr>
<td></td>
<td>Ratio systolic BP (night/day)</td>
<td>0.88 (0.72–1.03)</td>
<td>0.87 (0.67–0.98)</td>
<td>0.87 (0.72–1.19)</td>
</tr>
</tbody>
</table>

aMedian (range).
bMean

Night/day ratio not statistically different between groups.
Acute interstitial nephritis induced by glucosamine

Sir,

Acute tubulointerstitial nephritis (TIN) is an important cause of acute renal dysfunction resulting from immune-mediated tubulointerstitial injury. The commonest causes of TIN include drugs and infection. Acute interstitial nephritis accounts for up to 15% of patients hospitalized for acute renal dysfunction. Glucosamine is a relatively new alternative therapy for the treatment of osteoarthritis (OA). We present a case of possible glucosamine-induced TIN.

A 75-year-old man was admitted with a history of difficulty in passing urine, urgency, nocturia and hesitancy. There was no history of fever, rash or arthralgia. Past history was uneventful; he denied known drug allergy and the only medication he had been exposed to had been glucosamine (2–3 months) used for treatment of his osteoarthritis. General and systemic examination was unremarkable except for dehydration. Investigation revealed haemoglobin 10.3 g/dl; white cell count 15.1 x 10^9/l (neutrophils 13.98, eosinophils 0.02), platelets 179 x 10^9/l, sodium 140 mmol/l, potassium 4.3 mmol/l, urea 45.8 mmol/l, creatinine 97 μmol/l, bicarbonate 19 mmol/l, bilirubin 2 μmol/l, alanine transferase 36 IU/l, alkaline phosphatase 183 IU/l, albumin 26 g/l and CRP 221 mg/l. He was initially fluid-resuscitated aggressively and catheterized, draining approximately 2000 ml of urine. Despite the above, his renal functions deteriorated. During the same period, he also had a series of blood tests which included normal complement and negative serum electrophoresis, auto-immune screen, ANCA and anti-GBM. Ultrasound demonstrated normal sized kidneys with good cortical thickness and a simple cyst in the left kidney. Prostatic volume was mildly increased at 48 cm³ and prostatic specific antigen was within normal limits. Renal biopsy demonstrated a heavy mixed inflammatory cell infiltrate within the interstitium, suggestive of acute TIN. A minor degree of age-related atherosclerosis, involving the small and slightly larger blood vessels, was also noted. Glucosamine was discontinued and the patient received haemodialysis along with a short course of steroids. His symptoms improved significantly and he was dialysis-independent on discharge.

Drug-induced acute TIN is an inflammatory process involving the tubules and the space between the tubules and the glomeruli. It is mediated by T cell hypersensitivity reaction and cytotoxic T cell injury. Renal biopsy is the gold standard for diagnosis. Stopping the suspected medication forms the main component of treatment, with most patients recovering rapidly on withdrawal of the offending drug. Corticosteroid and immunosuppressants, in cases where there is no significant improvement in the renal function, may be of value. Recovery is more rapid in those individuals who have been exposed to the drug for less than 2 weeks, in comparison with those who have taken the suspected medication for more than 3 weeks.

Glucosamine is a commonly used alternative therapy in OA. Glucosamine is an aminosaccharide derived from chitin that takes part in the synthesis of glycosaminoglycans and proteoglycans by chondrocytes. It serves as a substrate for the biosynthesis of chondroitin sulfate, hyaluronic acid and other macromolecules located in the cartilage matrix. Experience with the use of glucosamine in OA is limited. There is no available literature reporting a direct link between glucosamine and nephrotoxicity, but there have been reports stating that additives like aristolochic acid, used in the preparation of glucosamine, can be nephrotoxic. Among the commonly known documented side effects of glucosamine, non-specific gastrointestinal tract symptoms lead the list, followed by worsening insulin resistance in diabetics. There have been no reports of glucosamine-induced TIN. In this case, there was no obvious precipitating factor other than glucosamine for the histological changes and impaired renal function. We therefore believe that glucosamine contributed to the pathogenesis of TIN in this case.

The results presented in this article, have not been published previously in whole or in part.

Conflict of interest statement. There is no conflict of interest to be reported by the authors.

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Transhepatic venous access as an alternative for Tesio catheter in the case of a patient on haemodialysis with antiphospholipid syndrome

Sir,

We report on a case of a patient with antiphospholipid syndrome with exhaustion of vascular accesses for haemodialysis. The transhepatic route through the suprahepatic vein...