Audit of antihypertensive treatment in patients with renal failure

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Abstract

Background. Recently, intensified antihypertensive treatment has been recommended for patients with proteinuric renal disease, and a target blood pressure of 125/75 mmHg has been proposed.

Methods. In a retrospective cross-sectional study, all consecutive patients with renal disease and reduced GFR seen in the renal outpatient clinic Heidelberg during a specified time period were analysed. Physicians administered antihypertensive agents according to their clinical judgment aware of recent recommendations, but without structured guidelines. The aims of the study were: (i) to monitor achieved blood pressure (clinic measurement, self measurement, ambulatory BP measurement); (ii) to monitor the number of antihypertensive medications required; and (iii) to analyse the factors which determine achieved blood pressure and the number of antihypertensive agents required.

Results. There were 201 non-transplanted patients, median age 60 years (range 20–86), 131 male, 70 female, median S-creatinine 2.33 mg/dl (1.4–10.9). Fifty-two of the patients had diabetes, 41 GN, 18 ADPKD, 17 vasculitis, seven reflux nephropathy, three analgesic nephropathy and 63 other or unknown renal diseases.

When the patients had originally been referred to the renal clinic, median clinic BP had been 160 mmHg systolic (104–260) and 95 mmHg diastolic (65–160). Under nephrological care, achieved clinic systolic (140–90–190) and diastolic BP values (85–45–130) were significantly \((P<0.0001)\) lower. Achieved BP was slightly \((r=0.23, P<0.05)\) correlated with age, was not significantly different between genders, and was not correlated to proteinuria, serum creatinine, renal disease or BMI. Average self measured BP values were not different from systolic and diastolic clinic BP values. Ambulatory BP values, however, were significantly \((P<0.0001)\) lower, e.g. daytime systolic BP 133 mmHg (107–171), diastolic 82 mmHg (65–97). A night-time decrease of BP \(\geq 15\%\) was seen in 18/25 patients only.

The median number of antihypertensive classes required was 3 (range 1–7) in non-diabetic and 3.5 (1–7) in diabetic patients, respectively. The number of antihypertensive classes was independent of serum creatinine, BMI or proteinuria, but was significantly \((P<0.01)\) higher in males (4; 1–7) than in females (3; 1–6) and correlated to age \((r=27, P<0.01)\).

Conclusions. The study (i) illustrates the difficulty to achieve recommended target BP in patients with renal failure, (ii) shows remarkably little white coat effect on clinic blood pressure, (iii) illustrates the value of ambulatory blood pressure measurement and (iv) documents the importance of multidrug antihypertensive treatment in patients with renal failure.

Key words: blood pressure; renal failure; antihypertensive treatment; ACE inhibitors; calcium channel blockers; progression of renal failure

Introduction

Antihypertensive treatment has been shown to reduce the rate of progression in patients with renal failure [1]. Available evidence suggests, (i) that ACE inhibitors are more efficacious in retarding progression than can be explained by lowering of systemic blood pressure alone [2,3] and (ii) that further lowering of blood pressure within the normotensive range according to WHO further reduces the rate of progression [4].

Several authors showed that patients with elevated S-creatinine require multidrug antihypertensive therapy [5,6], but systematic data concerning, (i) the number and types of antihypertensive classes necessary to achieve recommended target blood pressures and (ii) the factors determining the levels of achieved blood pressure (BP) and the number of antihypertensive agents required are currently not available.

In order to furnish such information we performed an audit, i.e. a retrospective analysis in a large representative sample of non-transplanted patients with different underlying renal diseases. The analysis included all patients who were seen during a defined time window in the renal outpatient clinic Heidelberg.
Patients and methods

Based on the patients' records, all patients with renal disease and elevated serum creatinine concentration (≥1.4 mg/dl) who had visited the outpatient clinic of the renal unit of the Department Internal Medicine Heidelberg between 1 March and 31 July 1997 were analysed according to a structured data evaluation sheet. Relevant demographic information is given in Table 1. In the outpatient clinic, all patients were seen by one of three senior nephrologists and only on occasion by junior nephrologists. Blood pressure was measured in the outpatient clinic according to the recommendations of the German High Blood Pressure League [7], i.e. seated after 3 min of rest with the cuff size appropriate for the upper arm circumference. Most patients (90%) monitored home blood pressure using electronic devices. During the above time period, ambulatory blood pressure, using Spacelab Medical 90207/32 apparatus (Redmond, WA, USA) had been measured in 25/201 patients.

In the outpatient clinic, patients were referred for evaluation and treatment of renal disease. Clinic blood pressure at the time when the patients had originally been referred to the renal outpatient clinic had been documented in all patients. None of the patients participated in a controlled trial to evaluate antihypertensive treatment according to protocol. Selection of the antihypertensive drugs was based on clinical judgment of the physician in charge of the patient. Unless indicated otherwise, all data are given as median and range. Statistical evaluation, i.e. linear regression or multivariate analysis, was performed using PC-Statistik 4.0, O. Hoffmann, Gießen 1997 package.

Results

Demographic information (Table 1)

The relevant patient characteristics are shown in Table 1. Of note is the high proportion of diabetic patients (more than 90% type II) which is characteristic of similar data from the same region [8]. Glomerulonephritis was biopsy-proven in 27 and suspected in 14 patients. Other diagnoses included nephrectomy (n = 12), renovascular hypertension (n = 7), myeloma (n = 5) and various urological disorders (n = 4). The cause was unknown in 35 patients.

Table 1. Demographic data and underlying diseases

<table>
<thead>
<tr>
<th>Demographic data</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>60 (20–86)</td>
</tr>
<tr>
<td>Gender</td>
<td>131 male/70 female</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 (18.3–40.2)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.33 (1.4–10.9)</td>
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</table>

<table>
<thead>
<tr>
<th>Underlying diseases</th>
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<tbody>
<tr>
<td>Diabetes type I and II</td>
<td>52</td>
</tr>
<tr>
<td>IgA glomerulonephritis</td>
<td>17</td>
</tr>
<tr>
<td>Other glomerulonephritides</td>
<td>24</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>18</td>
</tr>
<tr>
<td>ANCA-positive vasculitis</td>
<td>17</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>7</td>
</tr>
<tr>
<td>Analgesic nephropathy</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>63 (nephrectomy 12, renovascular 7, myeloma 5, various urological disorders 4)</td>
</tr>
</tbody>
</table>

Fig. 1. Clinic BP at referral and clinic BP during patient follow-up.

Table 2. Comparison of clinic BP and self-measured BP in all patients (n = 201)

<table>
<thead>
<tr>
<th></th>
<th>Clinic BP</th>
<th>Self-measured BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140 (90–190)</td>
<td>140 (110–180)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>85 (45–130)</td>
<td>85 (60–115)</td>
</tr>
</tbody>
</table>
Table 3. Comparison of clinic BP, self-measured BP and ambulatory BP in 25 patients who had ambulatory BP measurement during assessment period (1 March to 31 July 1997)

<table>
<thead>
<tr>
<th></th>
<th>Clinic BP</th>
<th>Self-measured BP</th>
<th>Ambulatory daytime BP</th>
<th>Ambulatory 24-h BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140 (120–190)</td>
<td>140 (120–160)</td>
<td>133 (107–171)</td>
<td>130 (107–163)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84 (60–115)</td>
<td>90 (70–95)</td>
<td>82 (65–97)</td>
<td>79 (64–97)</td>
</tr>
</tbody>
</table>

**Blood pressure correlates**

Achieved systolic clinic BP was not significantly related to gender (male patients median 140 mmHg systolic; range 90–190 vs female 140 mmHg; 110–190). By multivariate analysis, it was slightly related to age ($r = 0.23; P < 0.05$), but not significantly related to serum creatinine, proteinuria, underlying renal disease or BMI. Patients with diabetes mellitus, however, tended to have higher systolic BP, i.e. 145 mmHg; 90–190 vs 140 mmHg; 108–190 mmHg than non-diabetic patients and significantly ($P = 0.01$) lower diastolic pressures, i.e. 80 mmHg; 45–120 vs 90 mmHg; 55–130.

In women below the age of 52 years, the average age of German women at menopause, self-measured systolic blood pressure was significantly ($P = 0.01$) lower, i.e. 130 mmHg (range 110–170), than in women above 52 years, i.e. 140 mmHg (range 120–180 mmHg). There was no significant difference in diastolic blood pressure, i.e. 80 mmHg vs 82.5 mmHg.

**Requirement of antihypertensive agents**

Figure 2 shows that > 50% of patients needed at least three classes of antihypertensive agents. The number of classes of antihypertensive agents required ranged from 1 to 7. Table 4 shows the types of antihypertensive agents used. The most frequently used agents were diuretics in 77.1% (loop diuretics in 59 patients; thiazides in 56 patients and combination of the two in 40 patients). These were followed by ACE inhibitors/ANG II receptor blockers (64.2%), calcium channel blockers (103/116 patients had dihydropyridine type CCB), betablockers (39.8%), centrally acting antihypertensive agents (28.9%), and alpha adreno-

receptor blockers (16.9%). Minoxidil was required only in 2/201 of the patients.

By multivariate analysis the number of antihypertensive agents required was significantly ($P < 0.01$) higher in male patients, i.e. 4 (1–7) than in female patients, i.e. 3 (1–6). There was also a trend for diabetic patients to be treated with more classes of antihypertensive agents, i.e. 3.5 (1–7) vs 3.0 (1–7) in non-diabetic patients. There was a modest, but significant, correlation of the number of antihypertensive agents used to age ($r = 0.27, P < 0.01$), but not to serum creatinine, BMI, or protein excretion rate. In post-menopausal women, i.e. above 52 years, a significantly ($P = 0.001$) higher number of classes of antihypertensive agents, i.e. 3; 1–6, was required than in premenopausal women, i.e. 2; 1–5.

**Discussion**

There is consensus amongst nephrologists that effective antihypertensive treatment is the single most important modality of treatment in patients with renal disease. At least proteinuric renal disease effectively interferes with progressive loss of glomerular filtration rate. It is quite obvious, however, that the recommended goal blood pressure [9,10] is not easy to achieve. This may be due to a variety of reasons including patients non-compliance (which was not monitored in the study), intrinsic severity of hypertension in patients with renal disease, insufficient control of hypervolaemia, necessity to select multidrug therapy with complex schedules that tax the patients' cooperation and other factors.

Although we did not monitor patient compliance (apart from occasional measurements of plasma ACE activity in case of doubt in patients on ACE inhibitors), we monitored urinary sodium excretion which on average was 165 mmol/day, ranging from 65 to 497.
These figures indicate that patient compliance was suboptimal. We also emphasize that hormonal contraception was not used by any of the premenopausal women.

The gender difference of the number of antihypertensive agents required is in good agreement with numerous studies documenting a lower prevalence and severity of hypertension amongst premenopausal women. Some studies also showed less progression of renal disease in premenopausal, but not postmenopausal, women [11]. We do not have information on menopausal status in all women. The gender difference of blood pressure between premenopausal female and male renal patients may be even greater, even if adjusted for age. It is obvious that lower blood pressures may largely account for the more benign renal prognosis in women [12]. The present study also confirms numerous reports that at a given level of GFR, blood pressure tends to be higher in diabetic compared to non-diabetic patients, largely (but not exclusively) as the result of more severe hypervolaemia [13,14]. Their greater blood pressure amplitudes and lower diastolic blood pressures are in-line with observations that compliance of the central elastic arteries is more severely reduced in diabetic compared to non-diabetic uraemic patients [15]. This is an important aspect which may contribute to the high cardiovascular morbidity and mortality in patients with diabetic renal disease even prior to end-stage renal failure.

It is commonly stated that the prevalence and severity of hypertension increases with advancing renal failure. While this is undoubtedly true in untreated patients, it is of note that in this cohort of treated patients (i) achieved blood pressure and (ii) the number of antihypertensive agents required were not correlated to either serum creatinine concentration or rate of urinary protein excretion. Of note, advanced age was significantly correlated. These observations identify high risk groups. The present finding that hypertension is quite severe even in patients with modest elevation of serum creatinine is in-line with recent observations which document that a rise of blood pressure is noted in glomerulonephritic patients even when GFR is still normal [16].

Several aspects of the present study deserve comment. Almost all patients (more than 90%) had been on antihypertensive treatment at the time when they had been referred to the renal outpatient clinic. Nevertheless, in the renal outpatient clinic on average blood pressure could be lowered further by 20 mmHg systolic and by 10 mmHg diastolic, respectively. This is evidence that more rigorous attention to blood pressure control by nephrologists is effective even though BP lowering fell short of meeting recent recommendations [9]. Nevertheless, the study provides a powerful argument that dedicated outpatient clinics are necessary to improve management of patients with chronically progressive renal disease.

We emphasize that the difficulty of blood pressure control in outpatients is not unique to patients with renal disease as recently documented by the observation of Mancia [17] in patients with essential hypertension.

It is often stated that because of whitecoat hypertension [18] clinic blood pressure is an unreliable estimate of blood pressure load to target organs. Against this argument it is of note that on average clinic blood pressure and self-measured blood pressure values were in reasonable agreement. It would therefore be quite wrong for physicians to be complacent about elevated clinic blood pressure values in the mistaken opinion that they reflect a whitecoat phenomenon. The present analysis also vividly illustrates how important it is to monitor ambulatory blood pressure, since we found that one third of the treated patients clearly had insufficient lowering of night-time blood pressure values. This is of particular importance since irrespective of average blood pressure, an insufficient nighttime decrease of blood pressure (‘non-dipping’) is an independent predictor of progressive loss of renal function in diabetic [19] and non-diabetic [20] renal disease.

There has been some controversy about which antihypertensive agents are superior in attenuating progressive loss of renal function, particularly ACE inhibitors versus calcium channel blockers versus angiotensin receptor blockers. The present analysis confirms previous observations [5,6] and shows that only a small minority of patients with renal disease and elevated serum creatinine can be managed with one antihypertensive agent alone, i.e. only 15.4%. Combination of antihypertensive therapy is required in the large majority, rendering the above controversy largely irrelevant. In view of recent recommendations to use ACE inhibitors as the first line treatment [21], it may appear surprising that ACE inhibitors or angiotensin receptor antagonists were used only in 64.2% of the above patients, but this is mainly due to the fact that we hesitate to introduce de novo ACE inhibitors as the first line treatment once the GFR is 20–25 ml/min or below.

It is also surprising that a not negligible proportion of patients was left without diuretics. This was the result of side effects (cramps), electrolyte problems (hypokalaemia), suspected hypovolaemia because of increase in serum creatinine—but unfortunately, in many also the result of omission. A final point is the glaring non-uniformity of antihypertensive treatment even in an academic centre, despite continuous discussion amongst consultants and exchange of opinion, but in the absence of a structured approach. This observation illustrates that recent efforts to provide treatment guidelines are certainly welcome.

Finally, it is our personnel view that, unless there are contraindications, an ACE inhibitor/angiotensin receptor blocker should be the antihypertensive agent of first choice, at least unless serum creatinine concentration is above approximately 6 mg/dl. In the absence of contraindications these drugs should routinely be combined with a diuretic and recommendation of low salt intake. Those calcium channel blockers which do not cause tachycardia and sympathetic activation are
logical adjuncts if blood pressure is then not lowered to the recommended level. In view of the known sympathetic overactivity in renal disease, beta blockers should have high priority in the treatment of renal patients [22].

References

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