Altered blood pressure and renin responses to converting enzyme inhibition after aprotinin-induced kallikrein–kinin-system blockade

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Summary
1. The effect of aprotinin-induced blockade of the kallikrein–kinin system on haemodynamic and biochemical responses to converting enzyme inhibition by SQ 14 225 was evaluated in 26 patients with essential hypertension.

2. SQ 14 225 lowered blood pressure in high, normal and low renin hypertension. In low and normal renin patients, but not in high renin patients, the acute blood pressure-lowering effect of SQ 14 225 could be overcome by aprotinin. Aprotinin infusion produced small vasopressor effects in all groups of patients.

3. Aprotinin lowered the level of circulating active renin but not that of inactive renin.

4. It is concluded that in low and normal, but not in high, renin hypertensive patients activation of the kallikrein–kinin system is responsible for the acute blood pressure reduction observed with converting enzyme inhibition.

5. With long-term converting enzyme inhibition kallikrein–kinin system activation seems to play only a minor role.

6. The kallikrein–kinin system may be involved in the regulation of blood pressure.

7. There is no direct evidence of a participation of kallikrein in the activation of prorenin in vivo.

Key words: aprotinin, essential hypertension, converting enzyme inhibition, kallikrein–kinin system, renin.

Introduction
The orally active converting enzyme inhibitor SQ 14 225 (Captopril) (Ondetti, Rubin & Cushman, 1977) has been shown to lower blood pressure in patients with both essential and renovascular hypertension (Cody, Tarazi, Bravo & Fouad, 1978; Gavras, Brunner, Turini, Kershaw, Tiff, Cuttelod, Gavras, Vukovich & McKinstry, 1978; Johnston, McGrath, Millar & Matthews, 1979; Overlack, Stumpe, Heck & Krück, 1980). It has been postulated that the blood pressure changes with SQ 14 225 are mediated by a fall in angiotensin (ANG) II concentration (Case, Wallace, Keim, Weber, Sealey & Laragh, 1977).

However, interpretation of pressure responses to converting enzyme inhibition has been complicated, since angiotensin converting enzyme is identical with kininase II that degrades bradykinin (Erdös, 1977). Therefore, the possible hypotensive effect of increased bradykinin concentration through inhibition of kininase II-mediated degradation has to be taken into consideration (Williams & Hollenberg, 1977; Marks, Bing, Thurston & Swales, 1980).

The present study was designed to determine whether changes in renin–angiotensin- and/or kallikrein–kinin-system activity are responsible for the blood pressure-lowering effect of SQ 14 225. The kallikrein inhibitor aprotinin (Fritz, Fink & Truscheit, 1979) was used as a tool for dissecting out the contribution of the kallikrein–kinin system to blood pressure changes with converting enzyme inhibition.

Patients and methods
The study included 26 patients with essential hypertension. All patients had a diastolic pressure
greater than 100 mmHg. Three different groups of patients were investigated: nine untreated patients (group 1), seven patients who were pretreated with hydrochlorothiazide (50 mg/day for a period of 4 weeks) (group 2) and ten patients who were pretreated with SQ 14 225 (450 mg/day for a period of 4 weeks) (group 3). Patients of groups 1 and 2 received a single dose of 100 mg of SQ 14 225 on day 1 of the study. Two days later an infusion of aprotinin (Bayer AG, Leverkusen, F.R.G.) in a dose of $2 \times 10^6$ KIU (kallikrein inhibitor units) over 2 h was started 1 h before the administration of SQ 14 225. Patients of group 3 were infused with aprotinin after 4 weeks’ treatment with SQ 14 225. Two hours before starting the study procedures the patients had assumed the supine position. Blood pressure was recorded by a sphygmomanometer every 5–10 min for 2 h before and after the administration of SQ 14 225 and during the infusion of aprotinin. Blood was drawn before and 1 h after the administration of SQ 14 225 and before and 1 h after starting the infusion. Informed consent was obtained from all patients.

Plasma renin activity (PRA), inactive renin (trypsin activation) and the plasma concentrations of ANG II and aldosterone were measured respectively by the methods of Haber, Koerner, Page, Kliman & Purnode (1969), Sealey, Atlas, Laragh, Oza & Ryan (1979), Spech, Wernze & Weiss (1976) and Vetter, Vetter & Siegenthaler (1973). The activity of serum converting enzyme was determined by the method of Cushman & Cheung (1971). Data were analysed for statistical significance by Student’s paired t-test. Results are expressed as the means ± SEM.

Results

Mean values of systolic and diastolic blood pressure, PRA, inactive renin, serum converting enzyme activity and plasma concentrations of ANG II and aldosterone before and after administration of SQ 14 225 and aprotinin are summarized in Table 1. A single dose of 100 mg of SQ 14 225 lowered blood pressure in high, normal and low renin hypertension. In the two untreated patients with low PRA (< 0.3 ng of ANG I 3 h$^{-1}$ ml$^{-1}$ after 2 h recumbency) and the five with normal PRA but not in the two with high PRA (> 5 ng of ANG I 3 h$^{-1}$ ml$^{-1}$) after 2 h recumbency) or thiazide-stimulated PRA, this acute vasodepressor effect of SQ 14 225 was completely blocked by infusion of aprotinin. All groups of patients showed a small but consistent vasopressor response to aprotinin infusion. Aprotinin lowered basal and thiazide- or SQ 14 225-stimulated PRA, and blunted the increase of PRA after administration of SQ 14 225 in the untreated patients. With long-term inhibition of converting enzyme inactive renin increased significantly. It did not change during aprotinin infusion or with short-term administration of SQ 14 225.

Discussion

The present study shows that SQ 14 225 (Captopril)-mediated converting enzyme inhibition lowers arterial blood pressure in patients with high, normal and low renin essential hypertension. In normal and low renin patients, but not in high renin patients, the acute blood pressure response to SQ 14 225 could be completely blocked by aprotinin-induced kallikrein inhibition. On the other hand, blood pressure reduction with long-term converting enzyme inhibition could be overcome only in part by blockade of kallikrein. The demonstration that acute converting enzyme and kallikrein inhibition produced predictable and opposite effects on the blood pressure of normal and low renin hypertensive patients indicates that alterations in kallikrein–kinin-system activity were most likely to have been responsible for the haemodynamic changes observed with acute SQ 14 225 treatment. Moreover, the fact that aprotinin-induced kallikrein inhibition resulted in small but consistent vasopressor effects in all groups of patients, may be indicative of participation of the kallikrein–kinin system in the regulation of blood pressure. Similar changes in blood pressure after aprotinin have been reported by Lee, Kushiro, Gassia, Girolami, Lupu & Maxwell (1979) in one-clip, Goldblatt hypertensive rats. On the other hand, the lack of an effect of aprotinin on blood pressure reduction by SQ 14 225 in patients with high renin hypertension suggests a fall in ANG II concentration as the most important pressure-lowering mechanism of converting enzyme inhibition in this subgroup of patients. Similarly, with long-term converting enzyme inhibition kallikrein–kinin-system activation seems to play only a minor role in blood pressure reduction.

The present results provide some insight into the interrelation between kallikrein–kinin- and renin–angiotensin-system activation. From experiments in vitro it is known that kallikrein can activate prorenin (Sealy, Atlas, Laragh, Oza & Ryan, 1978; Derkx, Tan-Tjong, Man In’t Veld, Schalekamp & Schalekamp, 1979). Sealy et al.
<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Period</th>
<th>Blood pressure (mmHg)</th>
<th>PRA (ng of ANG I 3h⁻¹ ml⁻¹)</th>
<th>Inactive renin (ng of ANG I h⁻¹ ml⁻¹)</th>
<th>Converting enzyme (nmol min⁻¹ ml⁻¹)</th>
<th>ANG II (pg/ml)</th>
<th>Aldosterone (pg/ml)</th>
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<td></td>
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<td>Systolic</td>
<td>Diastolic</td>
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<td>1</td>
<td>9</td>
<td>Control</td>
<td>158 ± 4</td>
<td>109 ± 1</td>
<td>2.3 ± 0.7</td>
<td>14.9 ± 6</td>
<td>34.5 ± 3.6</td>
<td>10.2 ± 2.4</td>
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<td></td>
<td></td>
<td>SQ 14 225</td>
<td>137 ± 4</td>
<td>94 ± 2</td>
<td>4.6 ± 2.1*</td>
<td>17.6 ± 6.4</td>
<td>16.9 ± 3.4**</td>
<td>5.6 ± 2.6**</td>
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<tr>
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<td></td>
<td>Control</td>
<td>157 ± 6</td>
<td>109 ± 3</td>
<td>2.8 ± 0.7</td>
<td>17.6 ± 6.5</td>
<td>33.2 ± 3.6</td>
<td>9.5 ± 1.8</td>
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<td>Aprotinin</td>
<td>161 ± 9</td>
<td>113 ± 4*</td>
<td>1.6 ± 0.7**</td>
<td>17.7 ± 6.9</td>
<td>32.1 ± 3.7</td>
<td>8.9 ± 1.7</td>
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<td>Aprotinin + SQ 14 225</td>
<td>158 ± 11</td>
<td>110 ± 4</td>
<td>2.4 ± 0.7</td>
<td>16.6 ± 5.4</td>
<td>17.1 ± 4.7**</td>
<td>5.5 ± 1.6*</td>
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<td>Before thiazide</td>
<td>171 ± 6</td>
<td>116 ± 4</td>
<td>1.6 ± 0.5</td>
<td>---</td>
<td>29.5 ± 2.4</td>
<td>9.6 ± 2.7</td>
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<td></td>
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<td>155 ± 7†</td>
<td>106 ± 3†</td>
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<td>15.2 ± 2.4</td>
<td>28.4 ± 2.6</td>
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<td></td>
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<td>SQ 14 225</td>
<td>133 ± 7***</td>
<td>92 ± 3***</td>
<td>27.5 ± 14*</td>
<td>21.2 ± 6.5</td>
<td>7.3 ± 1.3***</td>
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<td>149 ± 5††</td>
<td>109 ± 4††</td>
<td>5.5 ± 1.2†</td>
<td>16.1 ± 2.5</td>
<td>27.9 ± 4.1</td>
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<tr>
<td></td>
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<td>Aprotinin</td>
<td>152 ± 7</td>
<td>115 ± 6*</td>
<td>4.1 ± 1.2*</td>
<td>19.3 ± 3.9</td>
<td>27.0 ± 3.9</td>
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<td>Aprotinin + SQ 14 225</td>
<td>133 ± 5**</td>
<td>97 ± 4**</td>
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<td>15.1 ± 3.4</td>
<td>7.5 ± 2.3**</td>
<td>8.1 ± 2*</td>
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<td>3</td>
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<td>Before SQ 14 225</td>
<td>175 ± 6</td>
<td>116 ± 3</td>
<td>2.2 ± 0.6</td>
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<td>36.5 ± 4.2</td>
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<tr>
<td></td>
<td></td>
<td>Control</td>
<td>133 ± 5†††</td>
<td>91 ± 5†††</td>
<td>17.6 ± 5.9††</td>
<td>22.9 ± 4.8†</td>
<td>18.4 ± 3.8†††</td>
<td>4.4 ± 0.9††</td>
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<tr>
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<td>Aprotinin</td>
<td>140 ± 6*</td>
<td>99 ± 4*</td>
<td>11.5 ± 5.5***</td>
<td>22.5 ± 4.9</td>
<td>19.6 ± 3.9</td>
<td>4.3 ± 0.5</td>
</tr>
</tbody>
</table>

Significance vs control data: *P < 0.05; **P < 0.01; ***P < 0.001. Significance vs pretreatment data (thiazide or SQ 14 225): †P < 0.05; ††P < 0.01; †††P < 0.001.
(1978) and Derkx et al. (1979) suggested that kallikrein-mediated liberation of active renin may be important in vitro as well. In the present study kallikrein inhibition by aprotinin was followed by a fall in PRA, but no change in inactive renin could be observed. Therefore, on the basis of this study, there is no direct evidence of a participation of kallikrein in the physiological activation of prorenin.

Acknowledgments

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References


