Angiotensin converting enzyme inhibitors and angiotensin II antagonists as therapy in chronic liver disease

Portal hypertension is the major complication of chronic liver disease and is associated with reduced survival. Pharmacological treatment is based on the premise that a sustained reduction in portal pressure will reduce the consequences of portal hypertension—that is, variceal bleeding, hepatic encephalopathy, and development of ascites.

Non-selective β-blockers have proved effective in reducing portal pressure by lowering splanchnic blood inflow and are used in primary and secondary prevention of variceal bleeding. However, the mean decrease in portal pressure in response to propranolol is only approximately 15% and one third of cirrhotic patients do not respond despite adequate blockade.

During the last decade, increased knowledge of the pathophysiology of portal hypertension has resulted in the use of new pharmacological targets; most importantly for the reduction of intrahepatic resistance, which is now recognised to be due in part to activated stellate cell contraction (myofibroblasts). These represent mesenchymal cells that reside in the perisinusoidal space of Disse and resemble tissue pericytes, a cell type with smooth muscle features that is thought to regulate blood flow via pericapillary constriction. During liver injury they undergo “activation”, characterised by production of increased amounts of extracellular matrix and are responsible for fibrosis.

Moreover, experimental data provide strong evidence that activated stellate cells are contractile and may regulate sinusoidal blood flow, especially in the injured liver.

The renin-angiotensin-aldosterone system (RAAS) is usually activated in patients with liver cirrhosis and this represents a homeostatic response to counterbalance the vasodilatation, arterial hypotension, and renal hyperfusion observed in portal hypertension. Plasma renin activity (PRA) is elevated in cirrhosis and is correlated with the hepatic venous pressure gradient (HVPG).

Angiotensin II (ANG-II) is considered a potential mediator of intrahepatic portal hypertension because its plasma levels are elevated in cirrhosis, and infusion of ANG-II induces a rise in portal pressure. Enhancement of the adrenergic vasoconstrictor influence on the portal system, direct contractile influence on activated stellate cells, and sodium and fluid retention induced by stimulation of aldosterone secretion are possible mechanisms that contribute to the portal hypertensive effect of ANG-II.

Hence, in theory, blockade of the RAAS by angiotensin converting enzyme (ACE) inhibitors/ANG-II receptor antagonists should be beneficial for improvement of fluid and salt secretion and reduce portal pressure in cirrhotic patients. ACE inhibitors block the RAAS preventing the conversion of inactive angiotensin I to active ANG-II, and may improve portal hypertension. However, concerns have been raised about their safety because of arterial hypotension and deterioration of renal function.

Orally active ANG-II receptor antagonists represent the most recent therapeutic development in the inhibition of RAAS. They are effective and safe in the control of systemic hypertension acting through specific AT1 receptors. Recently, the ANG-II receptor antagonists losartan and irbesartan have been studied in portal hypertensive patients with promising results.

We review the therapeutic effects of these drugs in cirrhotic patients.

Effects on renal function

SINGLE DOSE STUDIES (TABLE 1)

There are four studies involving 63 cirrhotics using ACE inhibitors. Captopril was used in 55 patients at doses ranging from 12.5 to 150 mg. In the first three studies captopril caused a significant reduction in glomerular filtration rate (GFR) with a consequent decrease in urinary volume and urinary sodium excretion, in association with significant decreases in mean arterial pressure (MAP). In the only randomised placebo controlled study, by Gentilini and colleagues, patients who had arterial hypotension after a single intravenous dose of captopril were excluded from the analysis so as to elucidate if the deleterious renal effects in the previous studies were secondary to arterial hypotension. However, captopril still induced a significant decrease in GFR and urinary sodium excretion in patients with or without ascites. Therefore, ANG-II contributes to the maintenance of renal haemodynamics in cirrhosis and consequently ACE inhibitors are harmful.

A subsequent study of 10 mg of enalapril in eight cirrhotic patients showed increased hourly urine volume and renal sodium excretion during the first two hours, but 24 hour urinary volume was unchanged.

Recently, Girgrah and colleagues evaluated the role of ANG-II in sodium homeostasis in nine preascitic cirrhotic patients using losartan, its receptor antagonist. A dose-response study showed that 7.5 mg was the optimal dose to produce natriuresis without systemic hypotension, normalising renal sodium without changes in systemic or renal haemodynamics. In the absence of GFR or renal plasma flow (RPF) changes, one would speculate that ANG-II has a direct sodium retaining effect on the renal tubule. However, baseline systemic ANG-II levels were significantly lower in preascitic cirrhotics compared with controls. The authors suggested that intrarenal production of ANG-II or increased sensitivity of preascitic cirrhotics to the sodium retaining effect of ANG-II would explain this discrepancy. Alternatively, losartan could have reduced portal pressure and thus improved sodium retention, without a direct effect on renal haemodynamics.

MULTIPLE DOSE STUDIES (TABLE 2)

In 1983, Saruta and colleagues used the ACE inhibitor SQ14225 in six cirrhotics for seven days. ANG-II and plasma aldosterone levels decreased and PRA increased markedly. Although systemic blood pressure was lowered, urinary sodium excretion increased significantly in five of the six patients.

Abbreviations used in this paper: ANG-II, angiotensin II; ACE, angiotensin converting enzyme; GFR, glomerular filtration rate; HSCs, hepatic stellate cells; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; PRA, plasma renin activity; RAAS, renin-angiotensin-aldosterone system; RPF, renal plasma flow; WHVG, wedged hepatic venous gradient.
of angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists on renal function, urine output, and sodium excretion

<table>
<thead>
<tr>
<th>Author/year</th>
<th>No patients</th>
<th>Ascites</th>
<th>Drug dose (mg)</th>
<th>Urinary Na output</th>
<th>Creatinine clearance or GFR (ml/min)</th>
<th>Urine volume (ml/day)</th>
<th>MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girgrah, 2000*</td>
<td>9</td>
<td>No</td>
<td>Losartan 7.5 oral</td>
<td>154 (8) to 202 (12) mmol/day</td>
<td>90 (9) to 92 (11) NA</td>
<td>NA</td>
<td>88 (3) to 84 (4)</td>
</tr>
<tr>
<td>Pariente, 1985†</td>
<td>6</td>
<td>Yes</td>
<td>Captopril 25 oral</td>
<td>In 4 remained &lt;5 μmol/min. In 2, drop from 198 and 200 to &lt;5 μmol/min</td>
<td>9.3 (23) to 71 (2.4)*</td>
<td>1.9 (0.4) to 1 (0.4) mmol/min*</td>
<td>87 (10.6) to 72.5 (7.3)*</td>
</tr>
<tr>
<td>Daskalopoulos, 1987‡</td>
<td>11</td>
<td>Yes</td>
<td>Captopril 50-150 oral</td>
<td>2.7 (1) to 0.48 (0.21) mmol/l*</td>
<td>Inulin clearance 73 (8) to 76 (7)</td>
<td>377 (55) to 182 (42) ml/min*</td>
<td>88 (1) to 74 (1)*</td>
</tr>
<tr>
<td>Ohnishi, 1990§</td>
<td>8</td>
<td>Yes</td>
<td>Captopril 50 oral</td>
<td>114.8 (12.2) to 85.6 (10.2) mmol/day</td>
<td>NA</td>
<td>1800 (170.6) to 1422 (134.2) ml/day</td>
<td>90.5 to 76*</td>
</tr>
<tr>
<td>Gentilini, 1993¶</td>
<td>30</td>
<td>Yes</td>
<td>Captopril 12.5 intravenous</td>
<td>43.8 (placebo) v 30.6 (drug) μmol/min*</td>
<td>108 (7) (placebo) v 78 (9) (drug)*</td>
<td>2.7 (0.7) (placebo) to 2.1 (0.4) (drug) mmol/min*</td>
<td>Reduction &lt;5</td>
</tr>
<tr>
<td>Saruta, 1983∥</td>
<td>6</td>
<td>No</td>
<td>SQ14225 75 mg oral</td>
<td>100 (5) to 165 (16) in 5 of 6*</td>
<td>Unchanged</td>
<td>1400 (210) to 1800 (180)*</td>
<td>92.6 (7) to 87 (7)</td>
</tr>
<tr>
<td>Brunkorst, 1989∥</td>
<td>14</td>
<td>Yes</td>
<td>Captopril 12.5 mg for 5 days then 25 mg for 5 days</td>
<td>70 to 125*</td>
<td>53.7 (7.8) to 66.9 (15.1)</td>
<td>Fluid balance: +200 to –600*</td>
<td>84 (2.9) to 78.4 (2.9)</td>
</tr>
<tr>
<td>Ibarra, 1992∥</td>
<td>9</td>
<td>Yes</td>
<td>Captopril 75 mg oral</td>
<td>36.7 (9.5) to 103 (13.8) 7 of 9 patients*</td>
<td>NA</td>
<td>NA</td>
<td>86.9 (2.6) to 80.2 (3.7)</td>
</tr>
<tr>
<td>Van Vliet, 1992∥</td>
<td>8</td>
<td>Yes</td>
<td>Captopril from 9 to 37.5 mg oral</td>
<td>72.8 (35.2) to 1128.5 (63.5) in 4 responders*</td>
<td>NA</td>
<td>1207 (456) to 1646 (395) in 4 responders*</td>
<td>79.8 (7.3) to 72.6 (9) in 4 responders</td>
</tr>
<tr>
<td>Wood, 1985∥</td>
<td>4</td>
<td>Yes</td>
<td>Captopril from 18.75 to 37.5 mg oral</td>
<td>14.25 to 6.5‡</td>
<td>70 to 46‡</td>
<td>NA</td>
<td>87 to 78‡</td>
</tr>
<tr>
<td>Tsai, 1996∥</td>
<td>25</td>
<td>Yes</td>
<td>Captopril 6.25 tds Placebo</td>
<td>20 (5) to 26 (6)</td>
<td>45 (11) to 40 (10)</td>
<td>790 (111) to 725 (85)</td>
<td>88 (3) to 86 (4)</td>
</tr>
<tr>
<td>Ohnishi, 1994∥</td>
<td>10</td>
<td>Yes</td>
<td>Enalapril 10 mg oral</td>
<td>73 to 110†</td>
<td>47 to 60‡</td>
<td>1800 to 2300*</td>
<td>NA</td>
</tr>
<tr>
<td>Amarapurkar, 1994∥</td>
<td>8</td>
<td>Yes</td>
<td>Enalapril 10 mg Placebo</td>
<td>46.5 (15.4) to 73.2 (19.7)*</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD).
NA, data not given in the studies or not applicable; GFR, glomerular filtration rate; MAP, mean arterial pressure.
*Statistically significant compared with baseline; †statistically significant compared with captopril.
‡All patients had ascites.

Six patients, and ascites improved but did not disappear. Since then, five studies comprising 60 patients with ascites have been reported using captopril (9–75 mg/day) given for 3–21 days. In three studies, captopril caused a significant reduction in body weight, enhancement of urinary sodium excretion, and improvement of fluid balance in the majority of patients. However, Wood and colleagues used captopril for three days in four patients with resistant ascites and reported falls in MAP with subsequent falls in GFR, decreases in sodium excretion, and no improvement in ascites. These authors suggested that ACE inhibitors have little place in the treatment of patients with resistant ascites and may be harmful. The only randomised placebo controlled study was performed by Tsai and colleagues and included 50 patients with ascites. PRA became significantly raised in the captopril group, and this was considered as adequate blockade of ACE. Nevertheless, there was no significant change in urine volume, creatinine clearance, or RPF, and the improvement in urine sodium excretion was not significant.

Enalapril was used in two small studies with 18 patients. In one, a significant increase in urinary volume and sodium excretion was seen. In both studies creatinine clearance improved significantly.

Evaluation of the above studies is difficult because most were neither placebo controlled nor randomised. Furthermore, as patient characteristics differed considerably between studies (for example, Child–Pugh class, presence of ascites, etc.), the effects of angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists on renal function, urine output, and sodium excretion cannot be evaluated comparatively.
of ascites, salt restriction, use of diuretics, and renal function impairment) it is difficult to make comparisons.

Single doses of captopril worsen renal function but this reflects only the immediate haemodynamic effects, which may not be the case with long term treatment. Indeed, some neurohormonal changes (for example, decrease in aldosterone levels) are evident only after long term treatment, as highlighted by Ohnishi and colleagues.

There are five multiple dose studies showing that captopril decreased renal sodium reabsorption to explain the positive effects of raised ANG-II levels in renal sodium handling and would not have deleterious effects on systemic haemodynamics.

**Effects on portal pressure**

ACE INHIBITORS

Captopril has been evaluated in four studies (table 3). In three (22 patients), captopril was given as a single oral dose. No significant change in HVPG was detected in any study. In addition, there was a small but significant decrease in MAP with deterioration of systemic haemodynamics. Ibarra and colleagues evaluated captopril after three weeks of administration, reporting a significant reduction in HVPG after three months of administration of enalapril in 12 cirrhotics undergoing long term sclerotherapy; no reduction in HVPG was found in 13 controls who received placebo. Systemic haemodynamics and liver function did not change.

The efficacy of enalapril in the blockade of RAAS and therefore in reducing portal pressure was evaluated in two small studies (table 3). Chiang and colleagues used 2.5 mg of enalaprilat, the active metabolite of enalapril, by intravenous infusion, in 20 patients with cirrhosis associated with hepatitis B. HVPG was reduced significantly within 30 minutes in 13 of 20 patients. Although MAP fell, liver and renal function did not change significantly. Svoboda and colleagues reported a significant drop in HVPG after three months of administration of enalapril in 12 cirrhotics undergoing long term sclerotherapy; no reduction in HVPG was found in 13 controls who received placebo. Systemic haemodynamics and liver function did not change.

Only two of the above studies were randomised with the use of placebo but the small number of patients with different clinical characteristics makes it difficult to generalise. However, similar to the absence of renal effects, captopril failed to reduce portal pressure in all four studies. Interestingly, enalapril proved effective in two small studies (32 patients) although there was a poor response in patients with severe liver dysfunction (Child

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**Table 3** Studies of the effects of angiotensin converting enzyme inhibitors on portal pressure

<table>
<thead>
<tr>
<th>Author/year</th>
<th>No patients</th>
<th>Drug dose (mg)</th>
<th>Duration</th>
<th>WHVP (mm Hg)</th>
<th>FHVP (mm Hg)</th>
<th>HVPG (mm Hg)</th>
<th>MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksson, 1984</td>
<td>7</td>
<td>Captopril 12.5–25 mg</td>
<td>Single oral</td>
<td>22 (2) to 19 (2)</td>
<td>8 to 5‡</td>
<td>14 (2) to 13 (2)</td>
<td>93 (3) to 79 (7)*</td>
</tr>
<tr>
<td>Pariente, 1985</td>
<td>6</td>
<td>Captopril 12.5 mg</td>
<td>Single oral</td>
<td>NA</td>
<td>NA</td>
<td>19.7 (3.6) to 18.8 (3.7)</td>
<td>87 (10.6) to 72.5 (7.3)*</td>
</tr>
<tr>
<td>Ibarra, 1992</td>
<td>9</td>
<td>Captopril 25 mg</td>
<td>Single oral</td>
<td>22.9 (2.7) to 20.7 (2.4)</td>
<td>15 (1.8) to 12.1 (0.9)</td>
<td>7.58 (1.5) to 8.58 (2)</td>
<td>86.9 (2.6) to 77 (1.9)*</td>
</tr>
<tr>
<td>Tsai, 1996</td>
<td>25</td>
<td>Captopril 18.75 mg</td>
<td>2 weeks</td>
<td>NA</td>
<td>NA</td>
<td>17.2 (1.3) to 17.5 (1.2)</td>
<td>88.3 (3) to 86 (4)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Placebo</td>
<td>2 weeks</td>
<td>NA</td>
<td>NA</td>
<td>17.6 (1.1) to 17.8 (1.1)</td>
<td>86 (2) to 85 (3)</td>
</tr>
<tr>
<td>Ibarra, 1992</td>
<td>9</td>
<td>Captopril 75 mg</td>
<td>3 weeks</td>
<td>22.9 (2.7) to 18.8 (2.9)</td>
<td>15 (1.8) to 9.4 (0.5)</td>
<td>7.6 (1.5) to 9.3 (2.7)</td>
<td>86.9 (2.6) to 80.2 (3.7)</td>
</tr>
<tr>
<td>Svoboda, 1995</td>
<td>12</td>
<td>Enalapril 20 mg</td>
<td>12 weeks</td>
<td>25.5 (4.8) to 21.3 (4.8)*</td>
<td>8.0 (2.8) to 8.6 (2.3)</td>
<td>17 (6) to 12.6 (3.4)*</td>
<td>14.1 (4.1) to 12.5 (3.8)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>22.8 (7.1) to 23.3 (6.7)</td>
<td>8.7 (4.3) to 8.2 (3.8)</td>
<td>14.2 (5.1) to 15.2 (3.4)</td>
<td>13.6 (4.2) to 12.8 (4.2)</td>
</tr>
<tr>
<td>Chiang, 1995</td>
<td>20</td>
<td>Enalaprilat 2.5 mg</td>
<td>Single intravenous</td>
<td>32.1 (5.1) to 25.6 (7.2)*</td>
<td>11.2 (3.7) to 10.7 (3.7)*</td>
<td>21 (4.3) to 16.1 (4.5)*</td>
<td>94.1 (11.2) to 85.6 (13.8)*</td>
</tr>
</tbody>
</table>

Values are mean (SD). NA, data not available; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure.

§Statistically significant.

‡Numbers obtained by measurement and/or calculation on figures.
C). This may be attributed to inadequate dosage to counteract the high RAAS in these patients. However, the subsequent changes in MAP after enalapril raise the possibility that the potential adverse effects may outweigh the potential benefits in larger doses. These opposite results for captopril compared with the enalapril studies are not easy to understand. In one study, enalapril was more effective in preventing the postural induced increase in aldosterone concentrations compared with captopril. This may reflect more complete inhibition of ACE. Whether such differences result in different clinical effects is debatable.

**ANG-II INHIBITORS**

During long-term ACE inhibition, alternative enzymatic pathways to ACE, such as trypsin and cathepsin, can also convert angiotensin I to ANG-II. This could explain why ACE inhibitors do not reduce portal pressure in cirrhotics. Moreover, ACE participates in the breakdown of bradykinin to inactive peptides. Accumulation of bradykinin after ACE inhibition would worsen the systemic hyperdynamic circulation in cirrhosis and thus outweigh the beneficial effects of ACE inhibitors on portal pressure. The development of specific antagonists of ANG-II receptors has renewed interest in the role of RAAS activation in portal hypertension and the potential benefit from its inhibition. Early in 1981, Arroyo and colleagues reported that intravenous infusion of saralasin (a short acting ANG-II antagonist) induced a significant reduction in WHVP but it correlated significantly with the decrease in ANG-II antagonist-induced reduction in WHVP. This may reflect the high RAAS in these patients. However, the subsequent changes in MAP after enalapril raise the possibility that the potential adverse effects may outweigh the potential benefits in larger doses. These opposite results for captopril compared with the enalapril studies are not easy to understand. In one study, enalapril was more effective in preventing the postural induced increase in aldosterone concentrations compared with captopril. This may reflect more complete inhibition of ACE. Whether such differences result in different clinical effects is debatable.

**Table 4  Studies of the effects of angiotensin II receptor antagonists on portal pressure**

<table>
<thead>
<tr>
<th>Author/year</th>
<th>No patients</th>
<th>Drug dose (mg)</th>
<th>Duration</th>
<th>WHVP (mm Hg)</th>
<th>FHVP (mm Hg)</th>
<th>HVPG (mm Hg)</th>
<th>MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arroyo, 1981</td>
<td>14</td>
<td>Saralasin 1–2.5 mg/kg/min Single infusion 17.2 (0.9) to 13.7 (0.9)* NA NA 76.8 (4) to 61.1 (5.9)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schneider, 1999</td>
<td>30 (HVPG ≥20 mm Hg) Losartan 25 mg 1 week 29.5 (3.8) to 18 (2.4) 4.8 (2.2) to 4.8 (2.4) 24.8 (2.6) to 13.1 (4.1)* 89.1 (6.8) to 86 (7.8)*</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>15 (HVPG ≥20 mm Hg) Placebo 1 week 28.3 (3.3) to 27.9 (3.8) 4.9 (2.2) to 4.8 (2.1) 23.9 (4.1) to 23.1 (4.2) 88.3 (5.5) to 88.6 (4.5)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>13 (HVPG &lt;20 mm Hg) Losartan 25 mg 1 week 22.1 (2.6) to 14.1 (2.9)* 4.2 (1.6) to 4.1 (1.5) 17.9 (1.4) to 10 (2.7)* 90.9 (5.5) to 87.4 (4.6)*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (HVPG &lt;20 mm Hg) Placebo 1 week 17.7 (1.3) to 16.9 (1.5) 4.3 (1.9) to 4.5 (1.9) 17.7 (1.3) to 16.9 (1.5) 93.3 (6.7) to 91.7 (4.5)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Debernardi-Venon, 1999</td>
<td>15 Irbesartan 300 mg 8 weeks NA NA 18.3 (4) to 14.5 (3.4)* NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schepke, 2000</td>
<td>145 Irbesartan 150 mg 1 week NA NA 18.3 (4) to 14.7 (3.7)* 81.3 (16) to 76.7 (14.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>16 Placebo 1 week NA NA 18.3 (4) to 17.6 (3.6) 81.8 (8.6) to 87.1 (9.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD). NA, data not available; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure.

*Statistically significant.

†One stopped due to side effects.

§Four stopped due to side effects.
ACE inhibitors for chronic liver disease

Angiotensin converting enzyme inhibitors and angiotensin II antagonists as therapy in chronic liver disease

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