Letters to the Editor

Angiotensin-converting enzyme inhibitors in heart failure: target dose prescription in elderly patients

SIR—Despite the benefits of therapy with angiotensin-converting enzyme (ACE) inhibitors for patients with heart failure, these agents are prescribed in only 5–10% of documented cases [1]. In younger people, they are frequently prescribed in doses below those used in clinical trials [2]. These trials have generally excluded subjects aged 75 or above, in whom heart failure is most common. However, the benefits for older patients have been illustrated by a 6-month mortality reduction of up to 40% [3].

A retrospective study was carried out comparing the discharge doses of four ACE inhibitor agents prescribed to patients aged 75 or over for heart failure with the maintenance dosage recommended in the *British National Formulary* [4]. Those receiving total daily doses below the specified target range were deemed to be sub-optimally treated. Patients with documented hypotension or deterioration in renal function considered to result from therapy were excluded. The results of the study are shown in Table 1.

![Table 1. Median discharge doses of angiotensin-converting enzyme inhibitors compared with target daily doses](image)

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Subjects</th>
<th>Dose (mg)</th>
<th>No. (and %) achieving target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean age (years)</td>
<td>Median</td>
</tr>
<tr>
<td>Captopril</td>
<td>50</td>
<td>79.8 (75–86)*</td>
<td>25</td>
</tr>
<tr>
<td>Enalapril</td>
<td>20</td>
<td>76.8 (75–80)</td>
<td>5</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>50</td>
<td>80.3 (75–82)</td>
<td>10</td>
</tr>
<tr>
<td>Perindopril</td>
<td>50</td>
<td>78.9 (75–82)</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td>79.3</td>
<td>-</td>
</tr>
</tbody>
</table>

* Range.

Discharge doses of heart failure treatment in 170 patients were identified from computer records. Seventy-six (45%) patients were discharged on the target dose of the prescribed agent and 55% with sub-optimal doses. The median dose was the target dose only in the case of perindopril, an agent with a single-step titration, where the regime was achieved in 37 (74%) cases. In the other agents (which have more complicated titration regimes), median doses identified were sub-optimal in 39 (33%) of 120 cases ($P < 0.001 \chi^2$ test)—at 50% (lisinopril), 33% (captopril) and 25% (enalapril) of target dose. Conversely, these drugs were prescribed in higher than recommended doses in 13 (11%) cases compared with none for perindopril ($P < 0.001$).

The question of optimal dosage of ACE inhibitors to treat heart failure is unresolved, but the beneficial effects of high-dose therapy are well established. To date, smaller trials have indicated that greater exercise capability [5], symptomatic improvement and survival [6] occur in subjects receiving high-dose rather than low-dose therapy; larger trials are in progress. However, many patients discharged from hospital on ACE inhibitor therapy for heart failure remain on unchanged doses and do not progress to the higher doses required for maintenance [7]. Although the reasons for this have not been defined, possible contributory factors include adverse effects on renal function, hypotension and its sequelae and the complex titration regimes of some agents.

For the present, higher-dose maintenance should remain the objective for all patients, particularly older people where the prognosis is worse. These patients, often frail or living alone, present the greatest practical difficulties in establishing optimal ACE inhibitor therapy and the selection of an agent with a simple titration regime may favour achievement of target dosage.

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Letters to the Editor


Tolerance to tacrine, arterial hypotension and leuko-araiosis in Alzheimer's disease

SIR—The baroreflex regulation of blood pressure is modulated by cholinergic systems [1]. Alzheimer's disease (AD) is more often associated with sympathetic dysfunction than fronto-temporal lobe dementia, in which the cholinergic system is relatively spared [2]. In patients with AD, orthostatic hypotension is associated with the severity of the cognitive decline—possibly because of chronic hypoperfusion of the white matter [3]. Orthostatic hypotension could also influence the response to cholinesterase inhibitors; Velnacrine non-responders had a more severe decrease in systolic postural blood pressure before treatment than responders [4].

Amar et al. [5] reported a high rate of withdrawal from tacrine in patients with AD with leuko-araiosis, especially because of agitation. We examined a possible relationship between tolerance to tacrine, orthostatic blood pressure and leuko-araiosis in patients with AD. Forty-one consecutive patients with AD with mild or moderate dementia were included. They were free from heart disease, diabetes mellitus or delirium. They were not taking any drugs with hypotensive side effects. Drug dosage had been stable for at least 1 month before the start of the study. Median age was 73.9 years (range 57-88), the median Mini-Mental State Examination score [6] was 19.6 (range 29-9) at baseline. Leuko-araiosis was assessed on computed tomography scan using Rezek's score [7].

Patients received 40 mg/day of tacrine for 6 weeks, 80 mg/day for 6 weeks, then 120 mg/day. Orthostatic hypotension (defined according to Bannister's criteria [8]) was noted at baseline and after 2 weeks of tacrine at 120 mg/day. The Mann-Whitney U-test was used for statistical analysis. Thirty-six patients were treated with tacrine without obvious side effects. Five patients (14%) were withdrawn prematurely: three because of gastritis and nausea, one because of agitation and one because of abnormal liver function tests. The age of withdrawn patients was higher than that of the others [80.2 years (73-88) versus 73.1 years (57-87); U = -1.97, P = 0.04]. The Rezek score did not differ between the groups: in withdrawn patients it was between 0 and 15 points. Seventeen patients had orthostatic hypotension: none was withdrawn. However, systolic blood pressure in supine position was significantly lower in withdrawn patients [123.6 mmHg (110-150) versus 142.6 mmHg (118-182); U = -2.43, P = 0.01]. Furthermore, orthostatic hypotension disappeared whilst on tacrine in 13 patients (42% versus 10%).

In conclusion, it appears that patients with low blood pressure have a lower tolerance of tacrine and that tacrine has an effect on orthostatic hypotension. A relationship between blood pressure dysregulation, cognitive decline, tolerance to anticholinesterase drugs in AD and white matter changes should be further investigated. Anticholinesterase drugs might also benefit patients with AD by decreasing orthostatic hypotension.

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