Acetylcholinesterase inhibition: a novel approach in the treatment of neurogenic orthostatic hypotension

W Singer, T L Opfer-Gehrking, B R McPhee, M J Hilz, A E Bharucha, P A Low

Background: Pharmacological treatment of orthostatic hypotension is often limited because of troublesome supine hypertension.

Objective: To investigate a novel approach to treatment using acetylcholinesterase inhibition, based on the theory that enhanced sympathetic ganglion transmission increases systemic resistance in proportion to orthostatic needs.

Design: Prospective open label single dose trial.

Material: 15 patients with neurogenic orthostatic hypotension caused by: multiple system atrophy (n = 7), Parkinson’s disease (n = 3), diabetic neuropathy (n = 1), amyloid neuropathy (n = 1), and idiopathic autonomic neuropathy (n = 3).

Methods: Heart rate, blood pressure, peripheral resistance index (PRI), cardiac index, stroke index, and end diastolic index were monitored continuously during supine rest and head up tilt before and one hour after an oral dose of 60 mg pyridostigmine.

Results: There was only a modest non-significant increase in supine blood pressure and PRI. In contrast, acetylcholinesterase inhibition significantly increased orthostatic blood pressure and PRI and reduced the fall in blood pressure during head up tilt. Orthostatic heart rate was reduced after the treatment. The improvement in orthostatic blood pressure was associated with a significant improvement in orthostatic symptoms.

Conclusions: Acetylcholinesterase inhibition appears effective in the treatment of neurogenic orthostatic hypotension. Orthostatic symptoms and orthostatic blood pressure are improved, with only modest effects in the supine position. This novel approach may form an alternative or supplemental tool in the treatment of orthostatic hypotension, specially for patients with high supine blood pressure.

Methods

Patient selection

Patients with neurogenic orthostatic hypotension were selected on the basis of the following criteria.

Inclusion criteria
- Adult men or women aged over 18 years.
- Orthostatic blood pressure fall of at least 20 mm Hg systolic or 10 mm Hg diastolic within three minutes of a 70° head up tilt.
- Presence of symptoms including lightheadedness, weakness, faintness, and blurred vision in the upright position, resolving when sitting or lying down.

Exclusion criteria
- Pregnant or lactating women.
- The presence of another cause of orthostatic hypotension.
- Failure of other organ systems or systemic illness that can affect the study results, autonomic function, or the patient’s ability to cooperate, including congestive heart failure, significant coronary artery disease, arrhythmia, renal disease, severe anaemia, hypothyroidism, and cerebrovascular accidents.

Maintenance of normotension in the standing position poses a substantial challenge for the cardiovascular system. Under normal circumstances, a significant fall in blood pressure can be prevented by a complex regulatory system comprising a series of neurohumoral mechanisms and cardiovascular reflexes, regulating vascular resistance, capacitance, stroke volume, and heart rate, with blood pressure as the controlled variable. Orthostatic hypotension is defined as a fall in blood pressure of at least 20 mm Hg systolic or 10 mm Hg diastolic within three minutes of a 70° head up tilt.

Patients with symptomatic orthostatic hypotension complain of lightheadedness, weakness, faintness, visual blurring, and impaired cognition in the upright position, resolving when sitting or lying down. In most patients, orthostatic hypotension is of neurogenic origin, resulting from impaired cardiovascular adrenergic function. The lesion can be postganglionic, as in pure autonomic failure and the autonomic neuropathies, or preganglionic, as in multiple system atrophy.

A major problem of current pharmacotherapeutic options is the non-selective elevation of blood pressure regardless of the body position, with supine hypertension as a common, troublesome, and typically dose limiting side effect. We hypothesised that as ganglionic transmission is low in the supine position and is greatly increased during orthostasis, enhancing ganglionic transmission by inhibiting acetylcholinesterase might selectively reduce orthostatic hypotension without causing significant supine hypertension. Our specific aim in this prospective study was therefore to evaluate the efficacy and characteristics of acetylcholinesterase inhibition in the treatment of neurogenic orthostatic hypotension.
Instantaneous heart rate was calculated from the RR interval. Baroreflex sensitivity was recorded using the formula: MBP = DBP + (SBP − DBP)/3.

Recording of heart rate and calculation of vagal baroreflex sensitivity

Instantaneous heart rate was calculated from the RR interval using continuous three lead ECG recordings. Vagal baroreflex gain was derived from RR intervals and systolic blood pressure values during five minutes of supine baseline recording using the sequence method. 11, 12

### Impedance cardiography

Changes in thoracic impedance during the cardiac cycle reflect changes in thoracic fluid volume and velocity, the main contributor being the thoracic aorta. 13 Impedance cardiography (BoMed NCCOM3 R-7, BoMed Medical Manufacturing, Irvine, California, USA) uses these dynamic changes of bioimpedance (sampled at 500 Hz) together with ECG and blood pressure recordings for a beat to beat calculation of cardiac output, stroke volume, end diastolic volume, and total peripheral resistance; these are normalised by body surface area to cardiac index, stroke index, end diastolic index, and peripheral resistance index.

### Respiratory excursion

Respiratory excursion was measured using a nasal thermistor. The respiratory signal was sampled at 230 Hz and the data point occurring coincident with the QRS pulse written to file.

### Data analysis

Cardiovascular variables at baseline and during tilt, as well as changes with tilt, were analysed off-line by a data analyst blinded to the treatment status. In order to minimise the influence of signal oscillations, 30 second averages of data were generated. The last 30 seconds before tilt were defined as baseline, and 30 seconds around minute 3 of tilt were defined as the tilt value. Paired tailed t test was used for statistical analysis of cardiovascular variables before and after treatment. The Wilcoxon rank-sum test was used to compare symptoms. For the evaluation of relations between variables, we used linear regression analysis and Spearman’s rank correlation.

All data are expressed as mean (SEM). Significance was accepted at the 5% level. Correction factors for multiple testing were not applied as the statistical interest greatly differed among comparisons. It was preferable to undertake multiple tests without corrections and observe the pattern of results. 19

### RESULTS

#### Patient characteristics

Demographic and clinical data, as well as findings of autonomic reflex testing (CASS scores), are summarised in Table 1. Eight men and seven women participated. Their mean (SEM) age was 56.2 (4.8) years.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Sex</th>
<th>CASS_adren</th>
<th>CASS_vagal</th>
<th>CASS_sudom</th>
<th>CASS_total</th>
<th>Duration of OH (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Multiple system atrophy</td>
<td>63</td>
<td>F</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>Multiple system atrophy</td>
<td>56</td>
<td>M</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Multiple system atrophy</td>
<td>76</td>
<td>F</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Multiple system atrophy</td>
<td>47</td>
<td>M</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>Multiple system atrophy</td>
<td>63</td>
<td>M</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>&gt;60</td>
</tr>
<tr>
<td>6</td>
<td>Multiple system atrophy</td>
<td>67</td>
<td>F</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>Multiple system atrophy</td>
<td>72</td>
<td>M</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>Parkinson’s disease with AF</td>
<td>68</td>
<td>M</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>Parkinson’s disease with AF</td>
<td>70</td>
<td>F</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>Parkinson’s disease with AF</td>
<td>69</td>
<td>F</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>Diabetic autonomic neuropathy</td>
<td>56</td>
<td>F</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Amyloid neuropathy</td>
<td>65</td>
<td>M</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>Idiopathic autonomic neuropathy</td>
<td>18</td>
<td>M</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>14</td>
<td>Idiopathic autonomic neuropathy</td>
<td>31</td>
<td>M</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>15</td>
<td>Idiopathic autonomic neuropathy</td>
<td>21</td>
<td>F</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

AF, autonomic failure; CASS_adren, composite autonomic severity scale, adrenergic function; CASS_sudom, composite autonomic severity scale, sudomotor function; CASS_vagal, composite autonomic severity scale, vagal function; F, female; M, male; OH, orthostatic hypotension.
Ten patients were diagnosed as having orthostatic hypotension of primary central origin (multiple system atrophy (n = 7) and Parkinson’s disease with autonomic failure (n = 3)); five had a peripheral cause (diabetic polyneuropathy (n = 1), amyloid neuropathy (n = 1), and idiopathic autonomic neuropathy (n = 3)). The CASS score was 5.7 (0.6), suggesting moderate to severe autonomic failure.

**Cardiovascular recordings**

**Supine rest**
Baseline variables were not significantly different before and after pyridostigmine (table 2), though a moderate but non-significant increase in supine blood pressure was observed after the drug in some patients.

**Head up tilt**
There was significant improvement in orthostatic blood pressure after pyridostigmine (table 2, fig 1). Peripheral resistance index in the upright position was also increased after pyridostigmine, while orthostatic heart rate was reduced. Cardiac index, stroke index, and end diastolic index did not change.

**Changes with tilt**
The blood pressure fall in the upright position was significantly attenuated after treatment with pyridostigmine (table 2, fig 1). There were no changes in heart rate, peripheral resistance index, cardiac index, stroke index, or end diastolic index after pyridostigmine.

**Orthostatic symptoms**
The improvement in orthostatic blood pressure was associated with amelioration of orthostatic symptoms (fig 2A). There was a significant correlation between symptomatic improvement and improvement in orthostatic blood pressure fall (fig 2B).

**Predictors of therapeutic response**
We sought to determine predictors of a good therapeutic response to acetylcholinesterase inhibition. No significant correlation was found between improvement in orthostatic blood pressure and the severity of cardiovascular adrenergic impairment (CASSadren), overall autonomic failure (CASStotal), pretreatment blood pressure fall, or age. The response to the drug was also not significantly different in orthostatic hypotension of primary central origin compared with peripheral origin. However, there was a negative correlation between vagal baroreflex gain and reduction in the orthostatic blood pressure fall (fig 3).

**Side effects**
A 63 year old man with multiple system atrophy reported sweating and perspiration starting about 30 minutes after taking pyridostigmine, lasting for about one hour.

A 76 year old woman with multiple system atrophy reported modest urinary urgency 30 minutes after taking pyridostigmine. Whether or not the drug was the cause of this event remains uncertain. The patient had experienced similar symptoms before. Urodynamic studies had revealed neurogenic bladder dysfunction.

A 70 year old woman with Parkinson’s disease and autonomic failure complained of modest abdominal cramping following a meal, five hours after taking pyridostigmine. Owing to the long latency between pyridostigmine intake and symptom occurrence, this problem could not be clearly attributed to the drug.

---

**Table 2** Cardiovascular variables in the supine position and during head up tilt before and after pyridostigmine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before pyridostigmine</th>
<th>After pyridostigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td>SBP [mm Hg]</td>
<td>155.5 (7.9)</td>
<td>170.9 (7.5)</td>
</tr>
<tr>
<td>MBP [mm Hg]</td>
<td>98.4 (3.7)</td>
<td>77.5 (4.0)</td>
</tr>
<tr>
<td>DBP [mm Hg]</td>
<td>70.4 (1.9)</td>
<td>58.7 (2.8)</td>
</tr>
<tr>
<td>PRI (dyn.s.cm⁻¹.m⁻²)</td>
<td>2361 (207)</td>
<td>1774 (173)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75.5 (3.4)</td>
<td>95.6 (7.6)</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>3.56 (0.28)</td>
<td>3.74 (0.39)</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>46.4 (2.6)</td>
<td>39.1 (3.6)</td>
</tr>
<tr>
<td>EDI (ml/m²)</td>
<td>73.2 (3.9)</td>
<td>71.6 (6.0)</td>
</tr>
</tbody>
</table>

Values are mean (SEM).
*Significant difference comparing variables for the same body position before and after pyridostigmine.
†Significant difference comparing position induced changes before and after pyridostigmine.
CI, index for cardiac output; DBP, diastolic blood pressure; EDI, index for end diastolic volume; HR, heart rate; MBP, mean blood pressure; PRI, peripheral resistance index; SBP, systolic blood pressure, SI, index for stroke volume.
Supine hypertension is one of the most common side effects of these drugs, because the elevation of blood pressure is not selective for body position. As supine hypertension is a common feature of orthostatic hypotension itself, it is also the most troublesome side effect, often limiting the value of these drugs.

The baroreceptor reflex plays a key role in blood pressure homeostasis. A fall in blood pressure leads to unloading of baroreceptors located in the carotid sinus and aortic arch, resulting in reduced traffic in glossopharyngeal and vagal afferents, activation of sympathetic outflow, and inhibition of cardiovagal neurones.

An ideal therapeutic concept of orthostatic hypotension would be to increase sympathetic outflow selectively in the standing position. A drug acting under baroreflex control would have minor effects in the supine position and would be most effective when the patient is standing. We present the novel concept of enhancing sympathetic ganglionic transmission by inhibition of acetylcholinesterase. Inhibiting this enzyme facilitates the transmission of impulses from cholinergic neurones across the synaptic cleft. As the preganglionic sympathetic neurone is cholinergic and the traffic through sympathetic ganglia is modest in the supine position and greatly increases with standing, we sought to achieve adrenergic vasomotor effects proportional to orthostatic needs.

Our data suggest that oral administration of 60 mg pyridostigmine is effective in the treatment of neurogenic orthostatic hypotension. Both standing blood pressure and peripheral resistance were significantly increased, while the orthostatic fall in blood pressure was attenuated. This improvement in blood pressure in the upright position was associated with significant amelioration of orthostatic symptoms. Furthermore, amelioration of orthostatic blood pressure and symptomatic improvement were significantly correlated. A moderate increase in blood pressure in the supine position after pyridostigmine was observed in some patients, but overall, supine blood pressure was not significantly affected, supporting our theory of a baroreflex controlled drug action. Cook et al even described a lowering effect of diastolic blood pressure after pyridostigmine, while Gemmill et al reported largely unaltered supine blood pressures following edrophonium injection. This fairly selective effectiveness of pyridostigmine in the standing position may be its most beneficial characteristic, bearing in mind the problem of supine hypertension.

Cardiac output, stroke volume, and end diastolic volume were not significantly altered in the lying or upright position. Supine heart rate was only mildly lower after pyridostigmine, but orthostatic heart rate was significantly reduced. While it is well recognised that acetylcholinesterase inhibition can induce bradycardia, our findings suggest that this effect is heart rate dependent, supporting the findings of other investigators on temperature regulation and exercise after pyridostigmine administration, and on the influence of pyridostigmine on heart rate responses to mental stress. This phenomenon might be explained by the dominating effect of pyridostigmine on muscarinic synapses being more evident in the upright position when there is vagal withdrawal and sympathetic activation. This mechanism seems to exceed an indirect ganglionic enhancement of sympathetic outflow to the heart.

Our concept of selective enhancement of ganglionic neurotransmission involves afferent as well as efferent baroreceptor pathways. As there was no correlation between drug response and the severity of autonomic—and in particular adrenergic—failure, we assume that the presence of only some preserved pathways is sufficient to improve vasomotor function significantly. Our findings of a negative correlation between baroreflex sensitivity and improvement in the fall in orthostatic blood pressure suggest that the response may even be better in patients with severely impaired baroreflex function.

Though published reports suggest a difference between central and peripheral autonomic failure in the supine noradrenaline response to acetylcholinesterase inhibition, supine blood pressure responses are not reported to differ significantly. While it is unclear whether such a difference in the noradrenaline response is also present in the upright position, we did not find a difference between primary central and peripheral autonomic failure in the orthostatic blood pressure response to pyridostigmine.

During this single dose trial, three patients (20%) reported modest side effects following pyridostigmine intake, including perspiration, urinary urgency, and abdominal discomfort. However, in two instances the symptoms could not be clearly attributed to the drug, and it remains possible that they were purely coincidental. Side effects of pyridostigmine are most
commonly related to overdosage and are mainly caused by activation of muscarinic receptors. Increased peristalsis resulting in abdominal cramps and diarrhoea is typically the most irritating side effect. 15–17 In most patients with neurogenic orthostatic hypotension, there is generalised autonomic failure, often including the gastrointestinal autonomic network. 15–17 We would therefore expect activation of muscarinic receptors to be beneficial by improving the common symptom of constipation in this patient group rather than being a significant source of adverse side effects. 15–17

Conclusions
Enhancement of ganglionic transmission by inhibition of acetylcholinesterase appears to be an effective and generally well tolerated method of treating neurogenic orthostatic hypotension. This novel approach could be of particular value for patients with supine hypertension. Further studies are needed to confirm the results of this open trial in a double blind protocol. It will be important to investigate potential side effects resulting in abdominal cramps and diarrhoea is typically the most irritating side effect. 15–17

References
Acetylcholinesterase inhibition: a novel approach in the treatment of neurogenic orthostatic hypotension

W Singer, T L Opfer-Gehrking, B R McPhee, M J Hilz, A E Bharucha and P A Low

J Neurol Neurosurg Psychiatry 2003 74: 1294-1298
doi: 10.1136/jnnp.74.9.1294

Updated information and services can be found at:
http://jnnp.bmj.com/content/74/9/1294

These include:

References
This article cites 24 articles, 5 of which you can access for free at:
http://jnnp.bmj.com/content/74/9/1294#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Hypertension (380)
- Movement disorders (other than Parkinsons) (766)
- Neuromuscular disease (1311)
- Peripheral nerve disease (631)
- Stroke (1449)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/