How should conversion between doxazosin formulations be carried out?

Expiry: 23rd August 2007

Background

Doxazosin is a long acting alpha-1 adrenergic blocker which is licensed for the treatment of hypertension. It is available as both immediate and modified release tablets. (1) The immediate release (standard) preparation is initiated at 1mg once daily increasing to a maximum of 16mg daily. The modified release preparation (doxazosin in the gastrointestinal therapeutic system, GITS, Cardura XL) is initiated at a dose of 4mg daily, increasing to 8mg daily as necessary. (1) This difference in dosing has led to confusion on how to convert patients from one formulation to another, mainly when switching from the modified release (GITS) preparation to the standard preparation.

Both NICE and the British Hypertension Society recommend that the current place of alpha blockers such as doxazosin in the treatment of hypertension is as fourth line treatment. (2;3) Current evidence does not support the use of alpha-blockers for initial treatment of hypertension. (2) Therefore a patient prescribed doxazosin is likely to be taking a number of other antihypertensive medications.

Doxazosin standard tablets are now classified as a generic Category M product in the Drug Tariff, whilst the modified release, (Cardura XL), is only available as a branded preparation and is classified as Category C. (4) The Department of Health calculates the reimbursement price of the category M drug based on information submitted by manufacturers. Category C drugs are priced on the basis of a particular brand or particular manufacturer. (4)

Answer

The pharmacological and pharmacokinetic effects of the doxazosin preparations are shown in table 1.

Table 1: Pharmacological and pharmacokinetic effects of the doxazosin preparations.

<table>
<thead>
<tr>
<th>Product</th>
<th>Bioavailability</th>
<th>Peak blood levels</th>
<th>Max. hypotensive effects</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardura XL (modified release)</td>
<td>54% (4mg XL)</td>
<td>8-9 hours post dose.</td>
<td>Reductions present throughout the day.</td>
<td>Terminal elimination half life is 22 hours.</td>
</tr>
<tr>
<td>(5)</td>
<td>59% (8mg XL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peak plasma levels are approximately 1/3 of those of the same dose of immediate release doxazosin tablets.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardura (branded immediate release)</td>
<td>~ 2/3 of the dose (6)</td>
<td>2-3 hours post dose.(7)</td>
<td>2-6 hours post dose.(7)</td>
<td>~ 22 hours, allowing for once daily dosing (6)</td>
</tr>
<tr>
<td>Doxadura (8) (a generic immediate release)</td>
<td>~63%</td>
<td>2-4 hours post dose.</td>
<td>2-6 hours post dose.</td>
<td>~22 hours, allowing for once daily dosing</td>
</tr>
</tbody>
</table>
Switching from modified release (GITS) to standard preparation

The initial dose of standard doxazosin is 1mg, to minimise the potential for postural hypotension and/or syncope. Dosage should then be increased to 2mg after 1-2 weeks and then 4mg if necessary, up to a maximum of 16mg daily.(6;8)

The following needs to be taken into consideration when switching a patient from the modified to the standard preparation:

- If used according to NICE/BHS guidelines, doxazosin therapy is additional to other antihypertensive medications.
- The patient will have been taking at least 4mg of doxazosin MR, as well as a number of other antihypertensive medications. Is it clinically reasonable to start standard doxazosin at a lower dose of 1mg in order to minimise potential postural hypotension etc?

There is very little published data comparing the modified release with the standard product. Os and Stokke assessed the effects of doxazosin GITS 4mg or 8mg daily with doxazosin standard 1-8mg daily, in an integrated analysis of two multicentre studies.(9) Over 700 patients were included in the analysis (392 with newly diagnosed or previously treated mild hypertension and 315 with mild-to-moderate hypertension). The maximum doxazosin dose in both trials was 8mg daily. [Doxazosin standard was started at 1mg at week 1, increasing to 2mg at week 2, 4mg at week 3 and then 8mg at week 5 if necessary. Doxazosin GITS was started at 4mg at week 1 and increased to 8mg at week 5 if necessary]. The primary efficacy parameter was the relative proportion of patients in the per-protocol (PP) analysis population (n=603) responding adequately to treatment at the final evaluable visit. All subjects in the trial were white.

The percentages of patients taking each dose at the end of the study are shown in table 2 and the changes in blood pressure are in table 3. Both products produced gradual but sustained reduction in blood pressure, with maximal effects reached after 5 weeks of therapy.

The number of patients achieving blood pressure control at the final visit in the PP analysis were 64% taking doxazosin GITS and 68% taking standard doxazosin. The estimated odds ratio was 0.83 (95% CI 0.594-1.170), within the pre-specified CI of equivalence. A reduction of ≥10mm Hg in sitting diastolic blood pressure was achieved by 69% of patients taking the GITS and 70% of patients taking the standard doxazosin preparations.

### Table 2: Percentages of patients taking each dose at study end

<table>
<thead>
<tr>
<th>PP analysis</th>
<th>1mg</th>
<th>2mg</th>
<th>4mg</th>
<th>8mg</th>
<th>Mean dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>1.6%</td>
<td>35.9%</td>
<td>27.0%</td>
<td>35.5%</td>
<td>4.7mg</td>
</tr>
<tr>
<td>Cumulative %</td>
<td>1.6%</td>
<td>37.5%</td>
<td>64.5%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>GITS</td>
<td>-</td>
<td>-</td>
<td>64.4%</td>
<td>36.6%</td>
<td>5.4mg</td>
</tr>
<tr>
<td>Cumulative %</td>
<td>-</td>
<td>-</td>
<td>64.4%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Changes in sitting and standing blood pressure (ITT) population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Doxazosin GITS</th>
<th>Doxazosin standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial mean sitting BP</td>
<td>159±15 / 100±4 mm Hg</td>
<td>158±15 / 101±4 mm Hg</td>
</tr>
<tr>
<td>Final mean sitting BP</td>
<td>146±16 / 91±8 mm Hg</td>
<td>146±14 / 90±7 mm Hg</td>
</tr>
<tr>
<td>Initial mean standing BP</td>
<td>159±16 / 103±6 mm Hg</td>
<td>159±16 / 104±6 mm Hg</td>
</tr>
<tr>
<td>Final mean standing BP</td>
<td>148±17 / 94±8 mm Hg</td>
<td>147±16 / 94±9 mm Hg</td>
</tr>
</tbody>
</table>
There was no significant difference between the responses from the patients taking the doxazosin GITS tablets (mean dose 5.4mg) and the standard preparation (mean dose 4.7mg). Of those patients on standard tablets who responded to a dose of 4mg or less (64.5% of the group), 56% of them needed a dose of 2mg/day, compared with 64.4% who responded with a doxazosin GITS 4mg/day dose.

Overall a similar number of patients in each doxazosin group suffered from adverse events (137, 43.1% in the GITS group and 135, 43.1% in the standard group). Fewer patients taking doxazosin GITS discontinued therapy (n=17, 5.3%) compared with those taking standard doxazosin (n=29, 9.3%).

In the absence of any firm recommendations from the manufacturers of Cardura XL, there are two possible strategies to convert patients from modified release to standard doxazosin:

1. Give half the dose of Cardura XL as standard doxazosin, i.e. 4mg XL switched to 2mg standard. There may be some patients who may require a higher dose.
2. Give the same dose as Cardura XL but there may be some patients who suffer orthostatic hypotension and need a lower dose.

The alternative is to comply with the licensed dosing recommendations and initiate therapy at 1mg daily, increasing at weekly/fortnightly intervals.(6,8)

**Switching from standard preparation to modified release (GITS):**

The initial dose of Cardura XL is 4mg once daily and this will control over 50% of patients with mild to moderate severity hypertension. If necessary, the dosage may be increased following this period to a maximum of 8mg once daily according to patient response. Clinically significant reductions in blood pressure are present throughout the day and at 24 hours post dose. The optimal effects of Cardura XL may take up to 4 weeks to be seen.(5)

Patients who are switched from standard doxazosin tablets to modified release should start treatment with Cardura XL 4mg/day, which should be titrated upwards to 8mg as necessary.(5)

**Cost**

Drug Tariff prices (August 2005) for doxazosin are as follows:(4)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Basic price (1 month treatment)</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxazosin 1mg</td>
<td>28x1mg = £1.64</td>
<td>M</td>
</tr>
<tr>
<td>Doxazosin 2mg</td>
<td>28x2mg = £2.04</td>
<td>M</td>
</tr>
<tr>
<td>Doxazosin 4mg modified release</td>
<td>28x4mg MR = £6.33</td>
<td>C (Cardura XL)</td>
</tr>
<tr>
<td>Doxazosin 4mg</td>
<td>28x4mg = £4.23</td>
<td>M</td>
</tr>
<tr>
<td>Doxazosin 8mg modified release</td>
<td>28x8mg MR = £12.67</td>
<td>C (Cardura XL)</td>
</tr>
</tbody>
</table>

**Summary**

Doxazosin standard tablets are now classified as Category M in the Drug Tariff and this makes it a less expensive treatment option than Cardura XL.

If patients are currently taking standard doxazosin and need to be transferred to Cardura XL, the initial dose is 4mg daily which can be increased to 8mg daily as necessary.
The recommendations for patients who are currently taking Cardura XL and are being switched back to standard doxazosin are less clear cut. The dose of standard doxazosin could be initiated at 1mg daily, as if starting therapy from scratch, or at half the Cardura XL dose. In both instances some patients will need a dose increase. Alternatively, the dose could be initiated at the same as the Cardura XL dose, but some patients may need a lower dose.

**Limitations**

- The suggested switch from modified to immediate release doxazosin is based on a trial which assessed comparable efficacy but not the implications of switching formulations. The trial assessed these agents as monotherapies – in the clinical setting most patients requiring doxazosin should also be taking other antihypertensive therapies.
- Pfizer only have recommendations for switching from the standard doxazosin preparation to the modified release (GITS) preparation, and not vice versa.(5)
- Although all subjects in the trial by Os and Stokke were white no apparent difference in blood pressure response of Caucasians and blacks (under the age of 65 years) has been seen in pooled analysis of hypertension studies.(7)

**References**


**Quality Assurance**

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Date Prepared
August 22nd 2005

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Date of check
August 23rd 2005

Search strategy
Please specify which of these are used if appropriate, (whether or not all of them yielded useful information) and add others if necessary:

- Embase: "((( Doxazosin-CM.DE. )) AND (Hypertension#.W..DE.) AND LG=EN AND HUMAN=YES) AND (Controlled-Release-Formulation#.DE.)":
- Medline: "(((Doxazosin#.W..DE.) AND (Hypertension#.W..DE.)) AND LG=EN AND HUMAN=YES) AND (DELAYED-ACTION-PREPARATIONS.DE.)":