How should conversion between doxazosin formulations be carried out?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

Before using this Q&A, read the disclaimer at www.ukmi.nhs.uk/activities/medicinesQAs/default.asp

Date prepared: July 2013

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. The immediate release (standard) preparation is initiated at 1mg once daily increasing after 1-2 weeks as necessary to 2mg once daily, thereafter 4mg once daily to a maximum of 16mg daily. The modified release preparation (doxazosin in the gastrointestinal therapeutic system, GITS, doxazosin XL) is initiated at a dose of 4mg daily, increasing to 8mg daily after 4 weeks if necessary.(1) There are a number of modified-release doxazosin preparations available, such as Cardura XL, Doxadura XL, Raporsin XL and Slocinx XL..(1) The GITS formulation was developed to enhance the pharmacokinetic profile allowing more uniform plasma levels and eliminating at least two dose titration steps that may be needed with standard doxazosin, whilst reducing the likelihood of significant first dose side effect. (2)

This difference in dosing has led to confusion on how to convert patients from one formulation to another.

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

Answer

The pharmacological and pharmacokinetic effects of some of the currently available doxazosin preparations are shown in table 1. The half-life of doxazosin is the same for both immediate- and modified-release preparations, allowing for once-daily administration. The advantages of the modified-release preparation are more consistent plasma levels and no dose titration phase.(4)

The effects of doxazosin GITS 4mg or 8mg compared with immediate-release doxazosin were compared in an integrated analysis of two multicentre studies (n=683 in the per protocol analysis). (4) The primary endpoint of both studies and of the combined analysis was the proportion of patients in the PP analysis with a sitting diastolic blood pressure (BP) ≤90mmHg or a decrease of ≥10mmHg measured 24-hours post dose. Both products produced gradual but sustained reduction in blood pressure, with maximal effects reached after 5 weeks of therapy. The blood pressure response to doxazosin GITS was achieved without the need for a titration period. Blood pressure control was achieved by similar proportions of patients in each group: 64% taking doxazosin GITS (mean dose 5.4mg) and 68% taking standard doxazosin (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 with doxazosin GITS discontinued therapy compared with standard therapy because of side-effects (5.3% versus 9.3%).
Table 1: Pharmacological and pharmacokinetic effects of some of the UK available 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) 59% (8mg XL)</td>
<td>8-9 hours post dose, Peak plasma levels are approximately 1/3 of those of the same dose of immediate release doxazosin tablets</td>
<td>Blood pressure reductions present throughout the day</td>
<td>22 hours</td>
</tr>
<tr>
<td>Doxdura XL (6)</td>
<td>54% (4mg XL) 59% (8mg XL)</td>
<td>6-8 hours post dose, Peak plasma levels are approximately 1/3 of those of the same dose of immediate release doxazosin tablets</td>
<td>Blood pressure reductions present throughout the day</td>
<td>Terminal elimination half-life is 22 hours</td>
</tr>
<tr>
<td>Raporsin XL (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slocinx XL (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardura (immediate release)</td>
<td>~ 2/3 of the dose</td>
<td>2-3 hours post dose</td>
<td>2-6 hours post dose</td>
<td>10</td>
</tr>
<tr>
<td>Doxadura (11) (immediate release)</td>
<td>~63%</td>
<td>2-4 hours post dose</td>
<td>2-6 hours post dose</td>
<td></td>
</tr>
</tbody>
</table>

Switching from modified-release 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. (9;11)

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?

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

1. Give half the dose of modified-release doxazosin 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 modified-release doxazosin 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. (9;11)

Switching from standard preparation to modified-release (GITS)

The initial dose of modified-release doxazosin is 4mg once daily and this will control over 50% of patients with mild to moderate severity hypertension. The optimal effects of doxazosin may take up to 4 weeks to be seen. 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. (5-8)

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

Summary

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

If patients are currently taking standard doxazosin and need to be transferred to modified-release doxazosin, the initial dose is 4mg daily which can be increased to 8mg daily as necessary.

The recommendations for patients who are currently taking modified-release doxazosin 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 modified-release doxazosin dose. In both instances some patients will need a dose increase. Alternatively, the dose could be initiated at the same as the modified-release doxazosin dose, but some patients may then need a dose reduction.

Limitations

- There are only recommendations for switching from the standard doxazosin preparation to the modified release preparations, and not vice versa. (5-8)
- This Q&A should be used in conjunction with UKMI Q&A 22, A comparison of doxazosin standard with doxazosin GITS.

References


(9) Summary of Product Characteristics: Cardura tablets 1mg, Cardura tablets 2mg. Date of revision of the text: 06/2012. Accessed via www.emc.medicines.org.uk on 02/07/2013. Pfizer Ltd.


Quality Assurance

Author

Contact
nwlh-tr.medinfo@nhs.net

Date Prepared
July 2013

Checked by
Alexandra Denby, London Medicines Information Service, Northwick Park Hospital

Date of check
23rd July 2013

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 )) AND (HYPERTENSION) AND (CONTROLLED-RELEASE FORMULATION))"
- Medline: "((DOXAZOSIN/) AND (*HYPERTENSION/) AND (DELAYED-ACTION PREPARATIONS/)"

Search strategy (cont.):