Barnsley Hospital NHS
NHS Foundation Trust

Changes to prescribing guidance for Simvastatin when used with interacting drugs

In August 2012 the Medicines and Healthcare Regulatory Agency (MHRA) issued updated advice on contraindications and drug interactions with simvastatin[1]:

- Simvastatin is contraindicated with ciclosporin, danazol and genfibrozil.
- The maximum recommended dose of simvastatin is 20mg daily when used concomitantly with amiodarone, amlodipine, diltiazem or verapamil.

The interaction with amlodipine, and reduction in simvastatin dose, is a new recommendation, whereas the other interactions are already well established. The interaction increases the risk of myopathy and/or rhabdomyolysis.

If you have a patient taking simvastatin and amlodipine concurrently, consider:

1. **Reducing simvastatin dose to 20mg** – most patients can be managed this way as the interaction with amlodipine leads to an increase in simvastatin exposure that is similar to taking simvastatin 40mg alone. 20mg is still an effective dose – simvastatin 20mg daily will deliver on average 90% of the lipid lowering efficacy of simvastatin 40mg daily (overall approximate increase in LDL cholesterol is 0.2mmol/L)

2. **Change to an alternative statin**
   - Atorvastatin is metabolised by the same CYP3A4 isoenzyme as simvastatin, although no changes have been made to the SPC in respect of this. No clinically significant interaction between amlodipine and atorvastatin has been reported. It appears that the risk of an interaction between amlodipine and atorvastatin is minimal. 10mg atorvastatin has approximately the same lipid lowering efficacy as simvastatin 40mg.

   - Pravastatin, fluvastatin or rosuvastatin are not appreciably metabolised by CYP3A4 and so far have shown little potential to interact in the same ways as simvastatin or atorvastatin. Whilst pravastatin and fluvastatin are available generically, please be aware that switching to rosuvastatin will cost significantly more.

3. **Staying on simvastatin 40mg** – discuss the risks and benefits of this 'off-label' option with the patient. Be aware that, due to the interaction with amlodipine, exposure to adverse effects is similar to that associated with simvastatin 80mg when given alone.

4. **Change to an alternative calcium channel blocker** - do not change therapy in patients who are well controlled with amlodipine. Altering the calcium channel blocker is clinically less desirable. Note: the maximum dose of simvastatin is also 20mg with verapamil and diltiazem.

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The MHRA advice is outlined in the table below, the recommendations highlighted in bold are significant changes from previous guidance and will impact on current prescribing practices:

<table>
<tr><th colspan="3">Drug interactions associated with an increased risk of myopathy/rhabdomyolysis</th></tr>
<tr><th>Interacting agents</th><th colspan="2">Prescribing recommendations</th></tr>
<tr><td>Itraconazole
Ketoconazole
Posaconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors (eg, nelfinavir)
Nefazodone
Ciclosporin
Danazol
Gemfibrozil</td><td colspan="2">Contraindicated with simvastatin – <u>recommend identifying patients and prescribe an alternative statin before next repeat prescription is issued.</u></td></tr>
<tr><td>Other fibrates (except fenofibrate)</td><td>Do not exceed 10 mg simvastatin daily</td><td rowspan="4">Recommend reviewing concomitant use at the patient’s next scheduled review, unless exhibiting symptoms of muscle toxicity</td></tr>
<tr><td>Amiodarone
Amlodipine
Verapamil
Diltiazem</td><td>Do not exceed 20 mg simvastatin daily</td></tr>
<tr><td>Fusidic acid</td><td>Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.</td></tr>
<tr><td>Grapefruit juice</td><td>Avoid grapefruit juice when taking simvastatin</td></tr>
</table>

These interactions are a result of inhibition of the CYP450 isoenzyme CYP3A4, leading to accumulation of simvastatin and a consequent increase in side effects, muscle toxicity being a particular concern. However, since the interacting drugs increase the overall exposure to simvastatin, there are few concerns over lower doses being less effective in lowering cholesterol levels.

Further information and advice can be obtained via the Medicines Information Service at Barnsley Hospital:

Tel: 01226 432857 or

Email: medicinesinformation@nhs.net

References:
1. Drug Safety Update August 2012, accessed online via www.mhra.gov.uk
2. BNF number 64, accessed online via www.bnf.org
3. Stockley’s Drug Interactions, accessed online via www.medicinescomplete.com

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