Clonidine and weight gain

Introduction

Clonidine is a central acting antihypertensive drug which has been approved for the Dutch market since 1968. Clonidine is an agonist of the α2-receptor and the imidazoline (I1) receptor in the central nervous system. Stimulation of these receptors results in several pharmacological effects, including a decrease of the blood pressure and heart rate. The innovator product Dixarit® (clonidine 0.025mg) is registered for migraine prophylaxis and menopausal flushing when estrogens are contraindicated or not tolerated and its registration is limited to treatment of adults and children of 12 year and older [1]. The innovator product Catapressan® (clonidine 0.15mg) is not available as tablet anymore. Generic products with clonidine (0.025, 0.1 and 0.15 mg) have a wider indication than Dixarit® and are also registered for hypertension and withdrawal reactions after cessation of opiates [2]. In clinical practice clonidine is used as well for indications like attention deficit disorder (ADHD), insomnia due to ADHD, alcohol withdrawal symptoms and as adjuvant to opiates for analgesia [3].

Reports

Until the 1st of June 2007 Lareb received six reports of weight gain associated with the use of clonidine, four of these reports concerned weight gain in children. The latency period varies from one month to one year. The outcome was reported in two cases, these patients lost weight after the dosage reduction of clonidine. The patient’s length was not reported.

Table 1. reports of weight gain associated with the use of clonidine

<table>
<thead>
<tr>
<th>Patient, Sex, age</th>
<th>Drug, daily dose Indication for use</th>
<th>Concomitant medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset, outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A M, 12</td>
<td>clonidine, 0.15 mg not specified</td>
<td>-</td>
<td>weight increased</td>
<td>some months, not reported</td>
</tr>
<tr>
<td>B M, 9</td>
<td>clonidine, 0.2 mg, not specified.</td>
<td>-</td>
<td>weight increased, 6kg (initial weight 53kg)</td>
<td>3 months, not reported</td>
</tr>
<tr>
<td>C F, 55</td>
<td>clonidine, 0.15mg hot flushes</td>
<td>pantoprazol, atenolol</td>
<td>weight increased, 5kg</td>
<td>1 month, weight decreased 2kg after dosage reduction</td>
</tr>
<tr>
<td>D F, 51</td>
<td>clonidine, 0.075 mg hot flushes</td>
<td>not reported</td>
<td>weight increased</td>
<td>not reported</td>
</tr>
<tr>
<td>E M, 6</td>
<td>clonidine, 0.15 mg ADHD</td>
<td>methylfenidate</td>
<td>weight increased</td>
<td>not reported, weight decreased 8kg after dosage decrease and increase of dosage methylfenidate</td>
</tr>
<tr>
<td>F M, 9</td>
<td>clonidine, 0.075 mg, pimozide 2.5mg, tics and restlessness</td>
<td>-</td>
<td>weight increased, 18kg (initial weight 30kg)</td>
<td>1 year, not reported</td>
</tr>
</tbody>
</table>
Other sources of information

SPC
Weight gain in relation to the use of clonidine is not mentioned in either the SPC of Dixarit®[1] nor any of the generic products containing clonidine [2]. Nausea and decreased appetite are listed as possible ADRs.

Prescription data
Clonidine is widely used in children, although it is not approved for children under age 12. The prevalence of stimulant use in children was investigated in the Netherlands, approximately 3 :1000 children, aged 0-19 years used clonidine in the North of the Netherlands between 1995 and 1999 [4]. The absolute number of users of clonidine in 2005 is shown in table 1.

<table>
<thead>
<tr>
<th>Age</th>
<th>0-4</th>
<th>5-14</th>
<th>15-24</th>
<th>25-44</th>
<th>45-64</th>
<th>65-74</th>
<th>75 +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine (Dixarit®) 0.025mg</td>
<td>0</td>
<td>2963</td>
<td>1114</td>
<td>1762</td>
<td>19892</td>
<td>1691</td>
<td>437</td>
</tr>
<tr>
<td>Clonidine (Catapresan®) 0.15 mg</td>
<td>*117</td>
<td>226</td>
<td>363</td>
<td>1106</td>
<td>262</td>
<td>238</td>
<td></td>
</tr>
</tbody>
</table>

*Approximately 40% of the children aged 5-14 who used clonidine Catapresan®, used clonidine Dixarit® as well in 2005 [6]

Literature
In the American SPC of Catapressan® TTS weight gain is listed as possible adverse drug reaction. This reaction would occur in about 1 in 100 patients [7]. Studies on clonidine with weight gain as primary outcome were not found. However Malone published a review article in which associations between medication and weight gain were investigated, she found a study in which weight gain was observed as secondary outcome of the use of clonidine [8].

Databases
On the 1st of June 2007 the Lareb database contained 6 reports concerning weight gain in association with clonidine (ROR=6.3; 95%CI 2.8 – 14.5).
The database of the Uppsala monitoring centre contains 28 reports of weight increase on clonidine (ROR 0.79; 95%CI 0.55-1.15)
The association between clonidine and weight gain is disproportionally present in the Lareb database, but not in the WHO database.

Mechanism
In early animal-experiments, clonidine induced hyperphagia and weight gain. The authors suggested that the appetite stimulation which was induced by clonidine is mediated through α2-receptors in the medial hypothalamus [9,10]. Non selective adrenergic stimulation does not cause hyperphagia as stimulation of β adrenergic receptors in the lateral hypothalamus suppresses feeding [11].
Discussion and conclusion

Lareb received six reports of weight gain, including four reports in which children were involved. In patients B and F the reported weight increases cannot be explained by normal growth. Patient F did not only use clonidine but also used pimozide which was reported as a possible suspected drug. The SPC of Orap® (pimozide) [12] does not mention weight gain as possible adverse drug reaction. Weight gain might be explained by drug induced appetite stimulation mediated through alpha 2-receptors. The American SPC of Catapresan® TTS mentions weight gain as common side effect, however the Dutch SPCs of Dixarit® and clonidine don’t mention this adverse drug reaction.

References
5. GIPdatabank, College voor zorgverzekeringen http://www.gipdatabank.nl. accessed 12-06-2007
6. Personal communication CVZ- GIPdatabank 12-06-2007
12. Dutch SPC Orap® (version date: http://www.cbg-meb.nl/IB-teksten/h06149-h06150.pdf)