1.1. SSRIs and hypoglycemia

Introduction

Serotonin reuptake inhibitors (SSRIs) are prescribed for the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder, panic disorder, generalized anxiety disorder, and posttraumatic stress disorder. The drug action is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT) [1]. In vitro and in vivo studies in animals suggest that SSRIs are highly selective serotonin reuptake inhibitors with minimal effects on norepinephrine and dopamine neuronal reuptake [1]. SSRIs on the Dutch market are citalopram (Cipramil®), escitalopram (Lexapro®), paroxetine (Seroxat®), fluoxetine (Prozac®), sertraline (Zoloft®) and fluvoxamine (Fevarin®). Venlafaxine (Efexor®) in a dosage less than 150 mg is also considered an SSRI.

The Dutch SmPC of paroxetine mentions the following in section 4.4 (Special warnings and precautions for use): In patient with diabetes treatment with an SSRI can alter the glycaemic control. It could be necessary to adjust the dosage of insuline and/or oral antiligicaemic drugs. Hypoglycemia is not mentioned in section 4.8 (Adverse Drug Reactions) of the SmPC or in section 4.5 (Interactions) [2].

The Dutch SmPC of citalopram does not mention hypoglycemia at all [3]. Escitalopram is the pure S-enantiomer (single isomer) of the racemic derivative citalopram [4]. The Dutch SmPC of escitalopram mentions hypoglycemia in section 4.4 but not in section 4.8 or in section 4.5 (Interactions) [4]. This is also the case for fluvoxamine [5], fluoxetine [6] and sertraline [7]. The Dutch SmPC of venlafaxine does not mention hypoglycemia at all [8].

The current observation describes the association between SSRIs and hypoglycemia.

Reports

Until December 01, 2008, the Netherlands Pharmacovigilance Centre Lareb received ten reports of hypoglycemia in association with various SSRIs and two additional in association with the use of venlafaxine. Cases of hypoglycemia with venlafaxine associated with intentional overdoses or rhabdomyolysis were not taken into account. Case G mentions hypoglycemia after the dose of the SSRI was decreased, an effect opposite to the other reports.

Table 1. Reports of hypoglycemia associated with the use of SSRIs.

<table>
<thead>
<tr>
<th>Patient, Number, Sex, Age</th>
<th>Drug, daily dose</th>
<th>Indication for use</th>
<th>Concomitant Medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset, Action with drug outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 74939</td>
<td>citalopram 20mg</td>
<td>depression</td>
<td>fluticasone a nasal inhalation 50mcg/do fl 150do, insulin aspart, omeprazole 20mg, oxazepam 10mg</td>
<td>hypoglycemia</td>
<td>2 hours citalopram discontinued, dosage of insulin altered, recovered</td>
</tr>
<tr>
<td>B 70574</td>
<td>escitalopram 10mg</td>
<td>depression, insulin aspart/insulin aspart protamine, diabetes mellitus</td>
<td>acetylsalicylic acid 80mg, nebulol 5mg, oxazepam 10mg, simvastatin 20mg</td>
<td>drug interaction, hypoglycemia</td>
<td>5 days escitalopram discontinued, unknown</td>
</tr>
<tr>
<td>Case No.</td>
<td>Sex</td>
<td>Age</td>
<td>Meds</td>
<td>Reactions</td>
<td>Notes</td>
</tr>
<tr>
<td>----------</td>
<td>-----</td>
<td>-----</td>
<td>------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>C 56288</td>
<td>F</td>
<td>36</td>
<td>alprazolam 0,25mg</td>
<td>erythrocine susp 250mg/5ml, glucagen</td>
<td>hypoglycemia (bloodglucose &lt; 2 mmol/l) 1 day citalopram and alprazolam discontinued, treated with glucagen-glucose 40%, recovered</td>
</tr>
<tr>
<td>D 56102</td>
<td>F</td>
<td>46</td>
<td>escitalopram 10mg</td>
<td>insulin, carbasalate calcium 100mg, folic acid 5mg, isosorbidemononitrate 60mg, insulin glargine, nitroglycerine, ranitidine 300mg, simvastatin 20mg, diltiazem 300mg, clorazepate 5mg</td>
<td>convulsions, hypoglycemia 18 days no change recovering at time of reporting (patient was hospitalized)</td>
</tr>
<tr>
<td>E 52374</td>
<td>F</td>
<td>27</td>
<td>fluoxetine 20mg</td>
<td>etoricoxib 90mg, bisacodyl 5mg, mebeverine 200mg, oxycontin 5mg, pantozole 40mg, montelukast 10mg, theophylline 250mg, tramadol 100mg</td>
<td>hypoglycemia (bloodglucose 3 mmol/l) Weeks after dose had increased from 20 mg to 80 mg unknown unknown</td>
</tr>
<tr>
<td>F 32262</td>
<td>F</td>
<td>75</td>
<td>paroxetine 20mg, insulin aspart/insulin aspart protamine</td>
<td>oxazepam 10mg</td>
<td>hypoglycemia not reported paroxetine discontinued recovered</td>
</tr>
<tr>
<td>G 28005</td>
<td>F</td>
<td>33</td>
<td>paroxetine 20mg</td>
<td>mixed anxiety &amp; depressive disorder, insulin</td>
<td>hypoglycaemic reaction (bloodglucose 2-3 mmol/l) not reported, reaction occurred after dose of paroxetine was decreased, no change not reported</td>
</tr>
<tr>
<td>H 23193</td>
<td>M</td>
<td>48</td>
<td>paroxetine 20mg</td>
<td>depressive episode, insulin, insulin isophane</td>
<td>hypoglycemia 5 days paroxetine discontinued recovered</td>
</tr>
<tr>
<td>I 17874</td>
<td>F</td>
<td>61</td>
<td>fluoxetine capsule 20mg</td>
<td>carbasalate calcium 38mg, triamterene 50mg, insulin isophane, insulin, omeprazole 20mg, oxazepam 10mg, flecainide 50mg, levothyroxine 0,100mg</td>
<td>hypoglycaemic reaction 1 day no change in fluoxetine, insulin dosage decreased, not reported</td>
</tr>
<tr>
<td>J 11279</td>
<td>F</td>
<td></td>
<td>fluoxetine 20mg</td>
<td>depressive episode</td>
<td>hypoglycaemic reaction 8 days Insulin dosage decreased not reported</td>
</tr>
<tr>
<td>K 62184</td>
<td>F</td>
<td>40</td>
<td>venlafaxine 75mg</td>
<td>non specified o.a.c.</td>
<td>drug interaction nos hypoglycemia 1 day no change not recovered</td>
</tr>
</tbody>
</table>
Other sources of information

**Literature**

Case reports suggest that antidepressants may interfere with blood glucose metabolism in patients with diabetes mellitus, by potentially increasing the risk of clinically relevant hypoglycemia [10-12]. In a nested case-control study among diabetic patients the risk of hypoglycemia requiring hospitalisation associated with the use of antidepressants was recently assessed [10].

Diabetic patients treated with insulin and/or oral antidiabetics were selected from the Dutch Pharmo system. Exposure to antidepressants was the primary determinant investigated. A trend for a higher risk on hypoglycemia was identified for antidepressants with high affinity for the serotonin reuptake transporter. The risk on severe hypoglycemia was increased after 3 years of use [10].

Also recently a case-control study was conducted based on spontaneous reports listed in the World Health Organization (WHO) Adverse Drug Reaction Database. Overall, the use of antidepressants was associated with hyperglycemia [ROR 1.52 (95% CI: 1.20–1.93)] and of hypoglycemia [ROR 1.84 (95% CI: 1.40–2.42)]. The association with hypoglycemia was most pronounced for antidepressants with affinity for the serotonin reuptake transporter. The results of this study strengthen the findings in individual case reports that the use of antidepressants is associated with disturbances in glucose homeostasis [12].

**Databases**

On December 1st 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports of hypoglycemia with the use of SSRIs. The reporting odds ratio (ROR) is 0.84 (95%CI 0.45 – 1.58).

The database of the WHO contained 521 reports of hypoglycemia or hypoglycaemic reaction for the various SSRIs on the Dutch market. The combined ROR = 0.51; 95%CI 0.47 – 0.56. The separate ROR’s for the various SSRIs are all non-significant. In addition the WHO database contained 64 reports of hypoglycemia in association with venlafaxine ROR = 0.59 (95%CI 0.46 – 0.75). These ROR’s would indicate a protecting effect.

On December 8, 2008, the Eudravigilance database contained 40 reports of hypoglycemia associated to the use of citalopram. Reactions occurred in 15 male and 25 female patients. Reported ages ranged from neonate age (twice) to 87 years. In four patients the hypoglycemia led to decease, 13 reactions were life-threatening. Hospitalisation was needed for 18 patients. Other causes of seriousness were reported in 11 cases.

**Mechanism**

In general hypoglycemia can be caused by regulatory, enzymatic or substrate defects. Iatrogenic hypoglycemia in diabetes mellitus is more appropriately viewed as the result of the interplay of relative or absolute therapeutic insulin excess and comprised glucose counterregulation. Insulin excess for example occurs when sensitivity to insulin is increased or endogenous glucose production is decreased [10]. In studies drugs with high affinity for the serotonin reuptake transporter were able to increase insulin sensitivity and insulin secretion, possibly leading to
(severe) hypoglycaemic reactions [10,13-15]. For example, in different studies in patients with type 2 diabetes mellitus and non-diabetic patients, the use of fluoxetine increased insulin sensitivity on the short term [13-15]. Besides, several animal studies revealed that the use 5-HT agents like of bupropion and sertraline increased insulin secretion in the short term [16,17]. In a clinical study by Briscoe et al. in which 12 nondiabetic persons underwent controlled hypoglycemia before and after six weeks of fluoxetine treatment; study subjects showed a 51% increase in epinephrine, a 23% increase in norepinephrine, a 59% increase in cortisol, a 6-fold lower requirement for exogenous glucose, and a 32% increase in endogenous glucose production during hypoglycemia with fluoxetine administration, suggesting that SSRI treatment may increase adrenal autonomic responses to hypoglycemia [18].

Users in the Netherlands

Table 2. Number of users of SSRIs in the Netherlands

<table>
<thead>
<tr>
<th>Drug</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>101,280</td>
<td>121,090</td>
<td>126,850</td>
<td>125,600</td>
<td>131,170</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>.</td>
<td>702</td>
<td>9,606</td>
<td>19,384</td>
<td>27,294</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>72,348</td>
<td>71,066</td>
<td>66,343</td>
<td>63,670</td>
<td>58,644</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>38,457</td>
<td>36,687</td>
<td>33,250</td>
<td>31,675</td>
<td>27,984</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>304,380</td>
<td>303,580</td>
<td>277,040</td>
<td>267,820</td>
<td>242,640</td>
</tr>
<tr>
<td>Sertraline</td>
<td>48,076</td>
<td>57,657</td>
<td>56,032</td>
<td>56,385</td>
<td>52,943</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>86,580</td>
<td>103,660</td>
<td>109,170</td>
<td>116,520</td>
<td>120,420</td>
</tr>
</tbody>
</table>

Source: GIP/College for health insurances 2008 Updated: 09-10-2008

Discussion

Lareb has received reports of hypoglycemia for the various SSRIs and venlafaxine. Although the association is not disproportionally present in both the Lareb as the WHO database, this association is well described in the literature. The number of reports suggests that this clinically relevant adverse drug reaction is not always recognized in daily practice.

Conclusion

In the SmPCs of most SSRIs altered glycaemic control is mentioned in the “Special warnings and precautions for use” section but should also be mentioned under the adverse drug reactions (section 4.8).

References

   http://memoboek.dynapaper.nl/38/glucose.html.
10. Derijks HJ, Heerdink ER, De Koning FH, Janknegt R, Klungel OH, Egberts AC. The association between
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11. David S. [SSRI should be considered as the cause of hypoglycemias which are difficult to explain]. Lakartidningen.
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    between antidepressant use and disturbances in glucose homeostasis: evidence from spontaneous reports. Eur J Clin
17. Gomez R, Huber J, Lhullier F, Barros HM. Plasma insulin levels are increased by sertraline in rats under oral glucose
18. Briscoe VJ, Ertl AC, Tate DB, Dawling S, Davis SN. Effects of a selective serotonin reuptake inhibitor, fluoxetine, on

This signal has been raised on February 2009. It is possible that in the meantime other
information became available. For the latest information please refer to the website of the MEB
www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).