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 antiglycaemic 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.

Patient, Number, Sex, Age	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 74939 F, 42	citalopram 20mg depression	fluticasone a nasal inhalation 50mcg/do fl 150do, insulin aspart*, omeprazole 20mg, oxazepam 10mg	hypoglycemia	2 hours citalopram discontinued, dosage of insulin altered, recovered
B 70574 F, 64	escitalopram 10mg depression, insulin aspart/insulin aspart protamine,diabetes mellitus	acetylsalicylic acid 80mg, nebivolol 5mg, oxazepam 10mg,ramipril 10mg, simvastatin 20mg	drug interaction, hypoglycemia	5 days escitalopram discontinued, unknown

C 56288 F, 38	alprazolam 0,25mg anxiety, citalopram 20mg depression, insulin lispro	erythrocine susp 250mg/5ml, glucagen	hypoglycemia (bloodglucose < 2 mmol/l)**	1 day citalopram and alprazolam discontinued, treated with glucagen-glucose 40%, recovered
D 56102 F, 46	escitalopram 10mg depression	insulin, carbasalate calcium 100mg, folic acid 5mg, isosorbidemononitrate 60mg, insulin glargine, nitroglycerine, ranitidine 300mg, simvastatin 20mg, diltiazem 300mg, clorazepate 5mg	convulsions, hypoglycemia	18 days no change recovering at time of reporting (patient was hospitalized)
E 52374 F, 27	fluoxetine 20mg	etoricoxib 90mg, bisacodyl 5mg, mebeverine 200mg, oxycontin 5mg, pantozole 40mg, montelukast 10mg, theophylline 250mg, tramadol 100mg	hypoglycemia (bloodglucose 3 mmol/l)**	Weeks after dose had increased from 20 mg to 80 mg unknown unknown
F 32262 F, 75	paroxetine 20mg insulin aspart/insulin aspart protamine	oxazepam 10mg	hypoglycemia	not reported paroxetine discontinued recovered
G 28005 F, 33	paroxetine 20mg mixed anxiety & depressive disorder, insulin		hypoglycaemic reaction (bloodglucose 2-3 mmol/l)**	not reported, reaction occurred after dose of paroxetine was *decreased,* no change not reported
H 23193 M, 48	paroxetine 20mg depressive episode, insulin, insulin isophane		hypoglycemia	5 days paroxetine discontinued recovered
I 17874 F, 61	fluoxetine capsule 20mg	carbasalate calcium 38mg, triamterene 50mg, insulin isophane, insulin, omeprazole 20mg, oxazepam 10mg, flecainide 50mg, levothyroxine 0,100mg	hypoglycaemic reaction	1 day no change in fluoxetine, insulin dosage decreased, not reported
J 11279 F,	fluoxetine 20mg depressive episode	insuline mixtard 30/70 penfill injection	hypoglycaemic reaction	8 days Insulin dosage decreased not reported
K 62184 F, 40	venlafaxine 75mg anxiety disorder, insulin detemir, insulin aspart	non specified o.a.c.	drug interaction nos, hypoglycemia	1 day no change not recovered

L 66420 M, 53	venlafaxine 75mg depression	patient had diabetes, drug use not specified	hypoglycemia	4 weeks unknown not recovered

* Insulin may also induce hypoglycemia, but was not in all cases reported as suspected drug. The Table presents the suspected drugs as classified by the reporter.
** Reference values for a lowered bloodglucose are given by the SAN online memobook (<3.1 mmol/l in plasma or <2.7 mmol/l in blood) [9].

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

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

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

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2. Dutch SmPC Seroxat®. (version date: 23-4-2008, access date: 1-12-2008) http://db.cbg-meb.nl/IB-teksten/h14668.pdf.
3. Dutch SmPC Cipramil®. (version date: 28-5-2008, access date: 1-12-2008) http://db.cbg-meb.nl/IB-teksten/h19593.pdf.
4. Dutch SmPC Lexapro®. (version date: 18-5-2008, access date: 1-12-2008) http://db.cbg-meb.nl/IB-teksten/h30494.pdf.
5. Dutch SmPC Fevarin®. (version date: 21-4-2008, access date: 1-12-2008) http://db.cbg-meb.nl/IB-teksten/h10245.pdf.
6. Dutch SmPC Prozac®. (version date: 16-5-2008, access date: 1-12-2008) http://db.cbg-meb.nl/IB-teksten/h19429.pdf.
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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).