

1.1. Escitalopram and headache

Introduction

Escitalopram (Lexapro®) is a selective serotonin re-uptake inhibitor (SSRI), it increases serotonin levels by blocking the reuptake of the neurotransmitter into the presynaptic neuron. It is the S-enantiomer of citalopram. Escitalopram has been approved for the Dutch market since April 2004. It is used for the treatment of *depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalised anxiety disorder and obsessive-compulsive disorder* [1].

The current observation describes the association between escitalopram and headache. Headache is only described in the SmPC of escitalopram as a withdrawal symptom which can occur when escitalopram is stopped abruptly [1]. The SmPC of citalopram (Cipramil®) mentions headache as an adverse drug reaction that is very common (incidence >10%) [2].

Reports

On October 10th, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of headache associated with the use of escitalopram. The reports are listed in Table 1.

Table 1. Reports of headache associated with the use of escitalopram

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 103365 F, 31-40 years, pharmacist	escitalopram 1dd 10 mg depression	mesalazine	headache, nausea, dizziness, feeling hot and cold	1-2 days, discontinued recovered
B 58737 M, 51-60 years, pharmacist	escitalopram 1dd 20 mg indication not specified	lorazepam, tramadol/ paracetamol	headache	hours after dose increase, unknown unknown
C 116637 F, 41-50 years, pharmacist	escitalopram 1dd 10 mg depression	paracetamol/codeine cetirizine	headache	hours, unknown unknown
D 90888 M, 31-40 years, specialist doctor	escitalopram 20 mg, dosage not specified depression	dasatinib	headache, fatigue, dizziness, abdominal pain, agitation	1 month, no change recovering

Some characteristics of the reports are discussed below:

Patient A had used mesalazine for several years.

Patient B experienced an increase in frequency of headache after dose increase of escitalopram (1 dd 10 mg to 1 dd 20 mg). The indication for the co-medication was not reported.

In patient C the concomitant medication had been used for several years and consisted of paracetamol/codeine, for pain not otherwise specified, and cetirizine. Patient D uses dasatinib for chronic myeloid leukaemia. However, the startdate is unknown.

Other sources of information

SmPC

The Dutch SmPC of escitalopram does not mention headache as an adverse drug reaction. Headache is only mentioned as a withdrawal symptom [1]. The US SmPC of escitalopram describes adverse events seen in adults with generalized anxiety disorder who received escitalopram 10 to 20 mg/day in placebo-controlled trials. Headache was seen in 24% of patients who received escitalopram (n=429) compared to 17% of patients who received placebo (n=427) [3]. The difference is statistically significant (Pearson Chi-Square test $p=0.012$). In the Dutch SmPC of citalopram, headache is mentioned with an incidence of >10% [2].

Literature

Wade *et al* [4] studied the efficacy, safety and tolerability of escitalopram in doses up to 50 mg in 60 primary care patients with major depressive disorder in an open label, pilot study. The most common adverse event was headache (35%). Emslie *et al* [5] studied the efficacy and tolerability of escitalopram in 312 adolescent patients with depression in a prospective, randomized, double-blind, placebo-controlled trial. Headache was reported in at least 10% of escitalopram treated patients. However, this did not statistically significantly differ from the placebo-treated patients.

In a double-blind placebo-controlled trial in 130 depressed patients aged 60 years or older treated with escitalopram, headache was reported in 19 % of the patients as treatment-emergent adverse event. This differed statistically significantly from placebo-treated patients (Pearson Chi-Square test $p=0.027$) [6].

Patients with migraine or chronic tension-type headache are more likely to suffer from a depression than individuals without headache [7].

Databases

On October 10th, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of headache associated with the use of escitalopram which was not reported disproportionally. The Reporting Odds Ratio (ROR) is 0.5 (95% CI 0.2-1.3). On the 10th of January 2012 this database contained 31 reports of headache associated with the use of citalopram.

Table 2. Reports of headache for escitalopram and citalopram in the Lareb database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Headache	Escitalopram	4	0.5 (0.2-1.3)
Headache	Citalopram	31	0.8 (0.6-1.1)

On the 6th of February 2012 the WHO database of the Uppsala Monitoring Centre contained 415 reports of headache associated with the use of escitalopram with a ROR of 1.2 (95% CI 1.1-1.3), which was disproportional. The WHO database contained 802 cases of headache associated with the use of citalopram. See table 3.

Table 3. Reports of headache for escitalopram and citalopram in the WHO database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Headache	Escitalopram	415	1.2 (1.1-1.3)
Headache	Citalopram	802	1.1 (1.0-1.1)

On November 24th 2011, the Eudravigilance database contained 208 reports of headache in association with escitalopram, which was not reported disproportionately (ROR = 1.1, 95% CI: 1.0 – 1.3). It concerned 141 females and 63 males. In four cases, the patient's sex was not reported, the median age was 46.5 years (range 10 – 82 years).

On the 10th of January 2012 the Eudravigilance database contained 207 cases of headache associated with the use of citalopram. See table 4.

Table 4. Reports of headache for escitalopram and citalopram in the Eudravigilance database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Headache	Escitalopram	208	1.1 (1.0-1.3)
Headache	Citalopram	207	0.9 (0.8-1.0)

Prescription data

The number of patients using escitalopram and citalopram in the Netherlands is shown in Table 5 [8].

Table 5. Number of patients using escitalopram and citalopram in the Netherlands between 2006 and 2010.

Drug	2006	2007	2008	2009	2010
Escitalopram	19,384	27,626	32,351	37,777	45,461
Citalopram	125,600	132,700	135,430	137,880	142,840

Mechanism

The role of serotonin in headache pathophysiology is not yet clearly understood. Serotonin modulates pain signaling within the dorsal horn. Serotonin can exert either antinociceptive or pronociceptive effects, depending upon the subtype and location of the receptors involved. Descending serotonergic pathway activation can promote nociceptive transmission by activating 5-HT_{2/3} receptors [9].

Discussion and conclusion

Lareb received four reports of headache associated with the use of escitalopram, one with a positive dechallenge. Headache is described in the US SmPC of escitalopram [3]. Several studies [4-6] published in the literature describe headache as the most common adverse drug reaction seen with escitalopram treatment. The association of headache with escitalopram use is supported by a statistically significant disproportionality in the WHO database. However, in the database of the Netherlands Pharmacovigilance Centre Lareb it was not reported disproportionately.

It has been implicated that alterations in serotonin neurotransmission play a role in the pathophysiology of headache. However, its exact mechanism is not yet fully understood. Headache is already described in the SmPC of citalopram. It should be considered to mention headache in the SmPC of escitalopram.

- Consider to mention headache in the SmPC of escitalopram

References

1. Dutch SmPC Lexapro[®]. (version date: 15-10-2010, access date: 10-10-2011) <http://db.cbg-meb.nl/IB-teksten/h30497.pdf>.
2. Dutch SmPC Cipramil[®]. (version date: 25-3-2011, access date: 10-10-2011) <http://db.cbg-meb.nl/IB-teksten/h19593.pdf>.
3. US SmPC Lexapro[®]. (version date: 12-5-2011, access date: 10-10-2011) http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021323s033,021365s024lbl.pdf.
4. Wade AG, Crawford GM, Yellowlees A. Efficacy, safety and tolerability of escitalopram in doses up to 50 mg in Major Depressive Disorder (MDD): an open-label, pilot study. BMC.Psychiatry 2011;11:42
5. Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. J.Am.Acad.Child Adolesc.Psychiatry 2009;48(7):721-9.
6. Bose A, Li D, Gandhi C. Escitalopram in the acute treatment of depressed patients aged 60 years or older. Am.J.Geriatr.Psychiatry 2008;16(1):14-20.
7. Smitherman TA, Walters AB, Maizels M, Penzien DB. The use of antidepressants for headache prophylaxis. CNS.Neurosci.Ther. 2011;17(5):462-9.
8. College for health insurances. GIP database. (version date: 2011, access date: 21-10-2011) <http://www.gipdatabank.nl>.
9. Argoff C. Mechanisms of pain transmission and pharmacologic management. Curr.Med.Res.Opin. 2011;27(10):2019-31.

This signal has been raised on February 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).