1.1. Paroxetine and (aggravation of) migraine

Introduction

Paroxetine (Seroxat®) was granted marketing authorization in 1991 in the Netherlands. Paroxetine is indicated for the use in *depression, obsessive-compulsive disorder, panic disorders with or without agoraphobia, social anxiety disorder/social phobia, generalized anxiety disorder and posttraumatic stress disorder* [1].
The efficacy of paroxetine in the treatment of the indications mentioned above 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). In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake [1].
Other SSRI's available on the Dutch market are citalopram (Cipramil®), escitalopram (Lexapro®), fluoxetine (Prozac®), fluvoxamine (Fevarin®) and sertraline (Zoloft®).

The current observation describes the association between paroxetine and (aggravation of) migraine.
Migraine is an episodic disorder, characterised by a severe headache generally associated with nausea, and/or light and sound sensitivity [2].
Once thought to be primarily vasculogenic resulting from constriction and subsequent dilation of cerebral blood vessels, migraine is now understood to be primarily neurogenic, and the observed vascular phenomena are secondary or epiphenomena to an underlying disturbance of the central nervous system (the trigeminovascular system in particular) [2,3].

Reports

On the 1st of February 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained eight reports of (aggravation of) migraine associated with the use of paroxetine. The reports are listed in table 1.

Table 1. Reports of (aggravation of) migraine associated with the use of paroxetine

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 11266 F, 31 – 40 years general practitioner	paroxetine 20mg od depressive episode	ethinylestradiole/ gestodene	migraine aggravated	1 week dose reduction not reported
B 18732 F, 31 – 40 years specialist doctor	paroxetine 20mg od depressive episode		migraine aggravated	not reported discontinued recovered
C 38500 F, 41 – 50 years specialist doctor	paroxetine 20mg od	ergotamine/ caffeine	migraine	not reported discontinued recovered
D 45171 F, 61 – 70 years pharmacist	paroxetine 20mg od depressive episode	conjugated estrogens, acetylsalicylic acid, oxazepam, metoprolol	migraine aggravated	several hours no change recovered

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 64503 F, 11 – 20 years physician	paroxetine 20mg od depression		migraine	2 years, after discontinuation not applicable unknown
F 81248 F, 41 – 50 years consumer	paroxetine 20mg od		therapeutic response unexpected with drug substitution, migraine	1 week unknown unknown
G 91619 M, 11 – 20 years pharmacist	paroxetine 20mg od depression		dizziness, bilirubin increased, migraine aggravated, nausea	8 week discontinued recovered
H 127252 F, 41 – 50 years general practitioner	paroxetine 20 mg od depression		migraine	14 day discontinued recovered, rechallenge positive

In the eight reports of migraine associated with paroxetine that Lareb received, a positive dechallenge was reported four times, once with a positive rechallenge. Some of the characteristics of the reports are described below.

Patient B realized that her migraine attacks had been more frequent and severe during the use of paroxetine after this drug was withdrawn. The migraine was treated with sumatriptan.
Patient C has a medical history of migraine in her family. The migraine was partly hormone-related (more severe in pre-menstrual phase). Ergotamine with caffeine was used in the same period as the paroxetine and withdrawn at the same moment as paroxetine. From the report it is not clear if this drug was used as concomitant medication or as a treatment for migraine caused by paroxetine.
Case E was sent to Lareb via the marketing authorization holder of paroxetine. The patient received paroxetine for three years between the age of 13 and 15. After discontinuation of paroxetine, the patient experienced migraine which had not recovered at the time of reporting.
In patient D the pre-existing migraine was the cause of her depression. In the report it's mentioned that it has been suggested to the patient that the dose of paroxetine could be lowered or paroxetine could be replaced by another antidepressant. However from the report it is not clear which action was taken.
In patient F the migraine started one week after paroxetine from the manufacturer Sandoz was replaced by paroxetine by Ratiopharm. The patient also reported migraine during previous use of venlafaxine. The patient described that the migraine was severe for three days (also with pain in the neck and backside of the head). The patient stayed in bed for one day and had to vomit.
Patient G recovered after discontinuation of paroxetine. Treatment with fluoxetine did not lead to migraine.
Patient H recovered after withdrawal of paroxetine. A rechallenge was positive. Paroxetine was continued after the rechallenge and the patient was treated with rizatriptan. The patient has a history of a cervix carcinoma (five years prior to the migraine) and was treated with unspecified chemotherapy and radiotherapy.

Other Sources of information

SmPC

In the Dutch SmPC of paroxetine (Seroxat®) headache is mentioned as an adverse drug reaction but migraine is not described [1].
The US SmPC of paroxetine (Paxil®) describes migraine as an infrequently occurring adverse drug reaction [4].

Literature

There are a number of case-reports in the literature describing the relationship between migraine and the use of SSRIs [5-7].
Delva et al. [5] report about a 44-year-old woman with migraine induced by several selective serotonin reuptake inhibitors. *Bickel et al.* [6] describe a case-report considering a 63-year old female patient with a history of migraine and major depression, who developed severe migraine attacks under treatment with the SSRI sertraline. After treatment with sertraline (50 mg daily) was started the patient developed the first severe migraine attack with unilateral headache, nausea, dizziness and vomiting during the second week of sertraline treatment (100 mg daily). Treatment with acetylsalicylic acid was ineffective but rizatriptan (10 mg) brought relief within two to four hours. With the use of metoprolol the frequency of the migraine headaches was reduced.
The authors further remark that associations of major depression and headaches have been observed [8] but that in this case episodes of depression and migraine attacks were not apparently correlated. They believe that the relapse of migraine headaches in this patient cannot be attributed to depression [6].
Alemdar & Selekler [9] report on a patient who experienced stereotypic migraine with aura attacks after taking citalopram for anxiety attacks.

Databases

On February 1st , 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained eight reports of migraine associated with the use of paroxetine. The association is not disproportional in the Lareb database for paroxetine or the SSRI's as a group. Table 2 shows the number of reports of migraine associated with the use of paroxetine and other SSRI's in the Lareb database.

Table 2. Reports of migraine for the SSRI's in the Lareb database

Drug	Number of reports	ROR (95% CI)
paroxetine	8	1.3 (0.7-2.7)
sertraline	1	-
escitalopram	0	-
fluoxetine	4	2.1 (0.8-5.6)
citalopram	5	2.0 (0.8-4.8)
fluvoxamine	1	-
SSRI's total	19	1.4 (0.9-2.3)

The WHO database of the Uppsala Monitoring Centre contained 496 reports of migraine associated with the use of paroxetine. The association is disproportional. Table 3 shows the number of reports of migraine associated with the use of paroxetine and other SSRI's in the WHO database.

Table 3. Reports of migraine for the SSRI's in the WHO database

Drug	Number of reports	ROR (95% CI)
paroxetine	496	3.4 (3.1-3.7)
sertraline	269	2.4 (2.2-2.7)
escitalopram	50	2.1 (1.6-2.7)
fluoxetine	240	1.5 (1.3-1.7)
citalopram	89	1.6 (1.3-2.0)
fluvoxamine	27	1.2 (0.8-1.8)
SSRI's total	1171	2.2 (2.3-2.5)

On 30 January 2012, the Eudravigilance database contained 85 reports of migraine associated with the use of paroxetine, of which 81 were classified as 'serious'. The reports concern 54 females and 21 males. In two cases, sex was not reported. The median age of the patients was 37 years (range 4 – 66 years). In five cases, age was not reported. Migraine was reported disproportionally (ROR = 2.7, 95% CI: 2.1 – 3.3).
On the 30th of January 2012 the Eudravigilance database contained several cases of migraine associated with the use of escitalopram, citalopram, paroxetine, fluoxetine, fluvoxamine and sertraline. See table 4. Overall the reporting odds ratio (ROR) for the association SSRI's and migraine was disproportional.

Table 4. Reports of migraine for the SSRI's in the Eudravigilance database

Drug	Number of reports	ROR (95% CI)
Paroxetine	85	2.7 (2.1 – 3.3)
Citalopram	17	0.8 (0.5 – 1.3)
Escitalopram	16	0.9 (0.6 – 1.5)
Fluoxetine	21	1.2 (0.8 – 1.8)
Fluvoxamine	2	0.3 (0.1 – 1.3)
Sertraline	31	1.4 (1.0 – 2.0)
SSRI's total	172	1.5 (1.3 – 1.7)

Prescription data

The number of patients using paroxetine in the Netherlands is shown in Table 5.

Table 5. Number of patients using paroxetine in the Netherlands between 2006 and 2010 [10].

Drug	2006	2007	2008	2009	2010
paroxetine	267,820	245,620	230,470	214,660	205,700

Mechanism

Pain transmission in the central nervous system is influenced by a wide range of neurotransmitters, including norepinephrine, dopamine, serotonin, γ-aminobutyric

acid (GABA), and enkephalins/endorphins. Increases in norepinephrine and dopamine have a migraine-provoking effect, whereas activation of other neurotransmitter receptors serves to inhibit migraine activity. Many of these same neurotransmitters are involved in mood and other emotional states, supporting a biological basis for comorbidity between migraine and mood disorders [11]. Serotonin (5-HT) levels play a role in both the pathogenesis of depression and migraine. In depression, the 5-HT levels are chronically lowered [6]. A chronically low serotonergic availability can increase sensitivity of trigeminovascular pathways that underlie migraine pain [11-13].

Several authors who have published case reports migraine associated with the use of SSRIs suggested that activation of 5-HT receptors can result in both cessation and initiation of migraine attacks [6,9]. According to *Alemdar & Selekler* [9] an imbalance between the serotonergic and cholinergic system could underlie the triggering effect on migraine of SSRIs. They suggested that the attack-precipitating character of SSRI's (which increases the synaptic serotonin amount) in the first days of treatment could be related to individual differences in expressions and/or sensitivities of 5-HT receptor subgroups in the brain. In long-term usage, SSRI's may induce gradual downregulation of 5-HT_2 receptors and could be effective in reducing the number and severity of migraine attacks [9]. *Bickel et al*. also pose that an initial administration of SSRI's might cause a rise of brain serotonin levels, inducing migraine attacks, while long-term administration might desensitize 5-HT-receptors [6].

Evidence supporting use of the selective serotonin reuptake inhibitors as headache preventives is poor [3]. However tricyclic antidepressants, which also block serotonin reuptake, are described as effective antimigraine prophylactic agents [3].

Class effect

Based on the cases in the literature and the reports of migraine for the SSRI's in the Lareb-, WHO- and Eudravigilance database it is possible that migraine is a class effect for all the SSRI's.

Discussion and conclusion

According to the proposed mechanism, the triggering of migraine attacks is most likely to occur within the first days after initiation of an SSRI. In the cases of migraine associated with paroxetine that Lareb received the reported latencies were relatively short in four of the eight cases (hours to two weeks) which is supportive of a causal relation. A latency of eight weeks was reported in one case and one patient experienced migraine after withdrawal of the SSRI. In two cases the latency was unknown. In four cases a positive dechallenge was reported, once with a positive rechallenge. In the US SmPC of paroxetine, migraine is mentioned [4].The relationship between paroxetine and migraine is further supported by a disproportionate reporting odds ratio in the WHO and Eudravigilance database. The described association is a new signal of (aggravation of) migraine with the use of paroxetine.

- New signal of (aggravation of) migraine associated with the use of paroxetine

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This signal has been raised on April 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).