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Serotonin Reuptake Inhibitors and Hyperprolactinaemia

A Case/Non-Case Study in the French Pharmacovigilance Database

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Abstract

Background: Hyperprolactinaemia is a common endocrinological disorder that can be caused by a variety of physiological and pathological conditions, although in a large proportion of cases hyperprolactinaemia is drug-induced. Serotonin reuptake inhibitors (SRIs) are reportedly associated with hyperprolactinaemia; however, the number of published cases in the literature is limited.

Objective: The aim of the study was to investigate the association between exposure to SRIs and the risk of reporting of hyperprolactinaemia in a spontaneous reporting database.

Methods: All cases of adverse drug reactions (ADRs) involving hyperprolactinaemia spontaneously reported to the French Pharmacovigilance Database from 1985 to December 2009 were reviewed. Cases of hyperprolactinaemia in SRI users were described. In a case/non-case analysis, the association between reported cases of hyperprolactinaemia and the use of SRIs was assessed by calculating reporting odds ratios (ROR) with their 95% confidence intervals (CIs).

Results: A total of 11 863 reports with SRIs were collected, of which 187 reported hyperprolactinaemia ADRs. Subjects were 39.7 ± 13.5 years of age on average and mainly female (71%). We observed an increased risk of reporting of hyperprolactinaemia with the use of SRIs as antidepressants (overall ROR 3.3; 95% CI 2.8, 3.8), particularly with fluvoxamine (ROR 4.5; 95% CI 2.8, 7.2), citalopram (ROR 3.9; 95% CI 2.6, 5.8), fluoxetine (ROR 3.6; 95% CI 2.8, 4.7) and paroxetine (ROR 3.1; 95% CI 2.3, 4.2). Duloxetine, milnacipran and sertraline were not associated with an increased risk of reporting of hyperprolactinaemia.

Conclusions: Treatment with SRIs is associated with an increased risk of reported hyperprolactinaemia. When investigating the aetiology of diagnosed hyperprolactinaemia, physicians should systematically enquire about treatment

with SRIs. The risk of hyperprolactinaemia should be mentioned in the labelling of all SRI compounds.

Background

Hyperprolactinaemia is defined as an elevated level of serum prolactin, in the absence of such conditions as pregnancy or lactation, and is caused by an increase in prolactin secretion from the pituitary gland.[1] It is a relatively common endocrine abnormality, with a prevalence of 1–1.5%, and may be caused by a number of pathological and pharmacological conditions. Increased prolactin levels can lead to clinical symptoms such as gynaecomastia, galactorrhoea and amenorrhoea.

In the majority of cases, hyperprolactinaemia is drug-induced. There is a long list of compounds that may lead to increased prolactin levels, among which antipsychotics are the most common. Dopamine receptor antagonists induce hyperprolactinaemia via the dopaminergic inhibition of prolactin secretion,[2] while other drugs can cause hyperprolactinaemia by reducing catecholamines in the hypothalamus, e.g. reserpine and tricyclic antidepressants. The main physiological means of controlling prolactin secretion is through the inhibiting action of dopamine, but also by gamma aminobutyric acid (GABA) [stimulatory effect], somatostatin (inhibitory effect), acetylcholine, noradrenaline (norepinephrine) and serotonin (stimulatory effect).[3]

Serotonin reuptake inhibitors (SRIs) feature among the drugs that can cause hyperprolactinaemia, although few clinical reports concerning this association are currently available. SRIs enhance serotonin activity by inhibiting CNS neuron serotonin reuptake, and they also interact with other neurotransmitters such as dopamine and noradrenaline. The largest study to date to investigate drug-induced hyperprolactinaemia was performed by Petit et al.,[4] who reported 159 cases, of which only 29 were caused by SRIs.

In this context, the aim of this case/non-case study was to investigate the association between exposure to SRIs and the reporting of hyperprolactinaemia using data from the spontaneous-reporting French Pharmacovigilance Database (FPVD).

Methods

The study used data from the FPVD of all adverse reactions occurring with commercially approved drugs in France. This database was established in 1985[5] to register all adverse drug reactions (ADRs) spontaneously reported by health professionals to the French Pharmacovigilance System, but not those reported to manufacturers. The database comprises data from 31 regional pharmacovigilance centres. Reports are reviewed by medically qualified personnel in the regional centres before being entered into the national database.

ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA®).[6] A serious ADR is defined as a reaction that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or any reaction that results in persistent or significant disability or incapacity, congenital anomaly or birth defect.

Observations reported from 1985 to December 2009 were reviewed using the following MedDRA® terms: 'hyperprolactinemia', 'prolactin increase', 'gynecomastia', 'galactorrhea' 'amenorrhea' or 'mastodynia'. We identified all reported cases of hyperprolactinaemia occurring with or without associated clinical signs (namely gynaecomastia, galactorrhoea, amenorrhoea or mastodynia). Exposed cases were defined as reports of hyperprolactinaemia (with or without associated clinical signs) occurring with any one or more of the SRIs currently marketed in France, namely fluoxetine, duloxetine, paroxetine, escitalopram, citalopram, venlafaxine, fluvoxamine, sertraline and milnacipran. All cases were assessed from the computerized data and reviewed by two physicians.

The case/non-case method was used to measure disproportionality of the combination between a drug and a particular ADR in the pharmacovigilance database. Cases were defined as reports corresponding to hyperprolactinaemia with or without associated clinical symptoms,

and non-cases as all other reported ADRs for the same period. These co-variates were analyzed.

For all cases, we studied the patient characteristics (age, sex and underlying disease use of drugs associated with hyperprolactinaemia) and the characteristics of the ADR (clinical symptoms, seriousness, level of biological prolactin, mean onset delay and evolution). Drugs associated with hyperprolactinaemia were based on an overview of drug-induced hyperprolactinaemia by Molitch.[7] Data in the FPVD are anonymous.

The reporting odds ratio (ROR) is the ratio of reporting of one specific event versus all other events for a given drug compound.[8] The 95% confidence intervals (CI) were calculated using the Woolf method.[9] A p-value <0.05 was considered statistically significant. All analyses were performed using SAS software version 9.1 (SAS System, SAS Institute Inc., Cary, NC, USA).

Results

Up to 31 December 2009, 369 778 spontaneous reports of ADRs had been recorded in the FPVD, among which 11 863 mentioned SRIs as the suspected medication. Overall, a total of 1910 cases of reported hyperprolactinaemia with or without clinical signs were identified, among which 187 concerned SRIs (clinical signs: amenorrhoea [n = 21] galactorrhoea [n = 102], gynaecomastia [n = 54] or mastodynia [n = 21]). The characteristics of the reported exposed cases are presented in table I, according to the type of SRI. The average age was 39.7 ± 13.5 years and 71.1% were female. The median onset delay of ADR was 3 months, with an interquartile range of 5 months (extremes 0–61 months). Mean onset delay differed significantly between type of SRI ($p < 0.0001$). Indeed, mean onset delays were higher for citalopram (9.7 ± 5.3 months) and venlafaxine (8.3 ± 6.4 months), and lower for milnacipran (1.2 ± 0.6 months) [table I]. No serious ADR was reported.

In seven cases, hyperprolactinaemia was associated with sexual disorders, mainly ejaculation disorders (fluoxetine [n = 2], fluvoxamine [n = 2] and citalopram, paroxetine and venlafaxine [n = 1 each]). No serious ADR was reported.

In all reports, only one SRI was mentioned. Other medications (in addition to SRIs) reported to be associated with increased prolactin levels were present in 67 reports (e.g. 32 cases were associated with antipsychotics, 11 with tricyclic antidepressants or monoamine oxidase inhibitors [MAOIs] and 11 with estrogens). When the evolution was known, all patients recovered after having stopped treatment. Positive rechallenge was observed in four cases (fluoxetine [n = 2], paroxetine [n = 2]). There were no cases of negative rechallenge.

Overall, we noted an increased risk of reporting of hyperprolactinaemia with SRI therapy (ROR 3.3; 95% CI 2.8, 3.9). This relation was significant for all SRI compounds except duloxetine, milnacipran and sertraline.

The ROR for hyperprolactinaemia with SRIs remained significant even after exclusion of the 67 cases with concomitant use of other drugs that could have been responsible for hyperprolactinaemia (ROR 2.1; 95% CI 1.8, 2.6).

Discussion

Our study shows that there is an increased risk of reporting of hyperprolactinaemia, with or without clinical signs, during treatment with SRI.

The regulation of prolactin in the body is extremely complex. Production and secretion of prolactin is controlled by neuroendocrine neurons in the hypothalamus, and prolactin homeostasis is maintained by achieving a balance between positive and negative stimuli deriving from both the external and endogenous environments. Prolactin is secreted by lactotroph cells in the pituitary gland and its secretion is affected not only by various physiological processes, but also by a wide range of drugs.

Dopamine is considered as the primary physiological prolactin inhibitor. It is secreted by the periventricular nucleus of the hypothalamus and when it reaches the pituitary gland, binds to dopamine D_2 receptors located on the lactotroph cells, thereby inhibiting prolactin secretion. Other neurotransmitters also influence prolactin secretion, such as GABA,[10] and the serotoninergic and noradrenergic systems.[2] Serotonin in particular has a major role in prolactin production

Table I. Description of cases of hyperprolactinaemia and crude reporting odds ratio (RORs) for the association between serotonin reuptake inhibitors and hyperprolactinaemia in the French Pharmacovigilance Database (FPVD)

Drug	All reports FPVD	Hyperprolactinaemia (n)	Sex (n [F/M])	Onset delay (mean ± SD [mo])	Age (mean ± SD [y])	ROR (95% CI)[a]
Citalopram	1 271	25	15/10	9.7 ± 5.3	39.4 ± 11.6	3.9 (2.6, 5.8)
Escitalopram	440	6	4/2	2.9 ± 1.0	39.8 ± 13.5	2.7 (1.2, 6.0)
Fluoxetine	3 161	57	39/18	6.7 ± 1.3	43.5 ± 14.1	3.6 (2.8, 4.7)
Fluvoxamine	789	18	12/6	5.3 ± 0.7	36.1 ± 11.4	4.5 (2.8, 7.2)
Milnacipran	341	3	2/1	1.2 ± 0.6	44.0 ± 17.6	1.7 (0.6, 5.3)
Paroxetine	3 113	49	41/8	3.9 ± 0.5	36.8 ± 13.9	3.1 (2.4, 4.2)
Sertraline	978	9	5/4	2.9 ± 0.4	39.4 ± 12.0	1.8 (0.9, 3.5)
Venlafaxine	1 545	19	14/5	8.3 ± 6.4	38.8 ± 14.2	2.4 (1.5, 3.8)
Total[b]	**11 863**[c]	**187**	**133/54**	**6.1 ± 10.4**	**39.7 ± 13.5**	**3.3 (2.8, 3.9)**

a 95% CI calculated using Woolf's method.[9]

b Including one reported case with duloxetine, a 36-year-old female, and onset delay 0.7 months.

c Including 225 reports with duloxetine.

F = female; **M** = male.

and secretion. The effect of serotonin is mediated through the production of, in the paraventricular nucleus, prolactin-releasing factors that affect prolactin secretion. However, the pathways connecting prolactin secretion and serotonin are numerous, while in the CNS the neurotransmitters serotonin and dopamine can also interact with each other.[11] Thus, drugs that block dopamine receptors, such as antipsychotics, or those that increase serotoninergic neurotransmission, can contribute to increased prolactin secretion.[12]

A wide range of drugs are reported to increase prolactin levels, including psychotropic drugs (particularly antipsychotics, tricyclic antidepressants, SRIs, MAOIs, opiates, amfetamines); antihypertensive agents (e.g. verapamil, methyldopa, reserpine); histamine H_2 receptor antagonists; antiemetics (e.g. domperidone, metoclopramide) and estrogens.[7,12]

Among these, the exact mechanisms by which SRI mediate their neuroendocrine effects on prolactin are not fully elucidated. SRIs elevate serotonin levels at the synapse through reuptake blockade of the serotonin transporters, and are also implicated in reducing dopamine activity via the serotonin 5-HT_2 receptor. All SRIs have affinity for dopamine, histamine and GABA receptors, but the level of affinity varies according to the molecule. Therefore, the mechanisms by which SRIs could interact with the secretion of prolactin are multifactorial and can engender varying levels of risk depending on the molecule.

Although it is widely acknowledged in the medical literature that SRI therapy can be associated with hyperprolactinaemia, specific scientific data in support of this hypothesis are sparse. In France, the majority of spontaneous reports registered in the national pharmacovigilance database are reported by health professionals, whereas the majority of data published in the literature are based on case reports.[13-32] However, the studies reported are non-controlled and have small sample sizes.[33-35] In a study by Amsterdam et al.,[33] in which 59 patients were treated, an increase in plasma prolactin levels was observed in paroxetine-treated patients only (n = 28); however, the number of patients treated with other SRIs was low. Muck-Seler et al.[35] did not observe any cases of hyperprolactinaemia in a study of 47 patients, of whom 15 were treated with paroxetine. In a literature review on the subject in 2006, Foley and Kast[36] reported that sertraline was the only SRI compound not to cause elevated prolactin levels. These conflicting results, therefore, do not provide any definitive response regarding the risk of hyperprolactinaemia with SRIs. The complexity of the mechanisms regulating prolactin secretion, as well as the multitude of physiological and pathological factors that can modify its secretion, make it very difficult to es-

tablish a causal link with medications on the basis of only a few isolated cases.[37]

Nevertheless, given that France has the highest level of antidepressant consumption in the world,[38] this makes it possible to collect a considerable number of reported ADRs with clinical signs related to hyperprolactinaemia. The results of our study, with 187 cases, are in contrast with the results of an earlier study published in 2003 by Petit et al.,[4] where sertraline was shown to be associated with an almost 16-fold increase in the risk of hyperprolactinaemia, whereas in our study we did not observe any significant relation between the use of sertraline and the likelihood of reporting an ADR involving hyperprolactinaemia. Similarly, we observed a significant, 4-fold increased risk of reporting hyperprolactinaemia with citalopram, whereas Petit et al.[4] did not observe any increase in risk with this compound. Indeed, we observed an increase in the risk of reporting hyperprolactinaemia, with or without clinical signs, with the majority of SRIs, underlining that the risk may vary across products; this warrants further investigation.

To the best of our knowledge, this epidemiological study based on the FPVD is the largest study to date to explore the relation between SRI treatment and the reporting of ADRs involving hyperprolactinaemia, associated or not with clinical signs.

Some limitations of this study deserve to be mentioned. There are several potential pitfalls inherent to the use of disproportionality measures in spontaneous reporting databases to estimate risk. For example, selection bias due to spontaneous reporting[39,40] (such as underreporting and notoriety bias), as well as Weber's effect,[41] could have altered our results. However, as stated by Mannesse et al.,[42] non-selective underreporting and overreporting does not have any significant influence on the ROR estimation, since it affects both the numerator and the denominator.

Conclusions

The present study demonstrates an association between the use of SRIs and reporting of hyperprolactinaemia. The data indicate that SRI-induced hyperprolactinaemia is a class-related effect. However, the mechanism of action of the potential link between SRIs and prolactin levels remains to be fully elucidated. It is likely that blockade of dopaminergic receptors is one of the components of the mechanism, but alone cannot account for the differences in risk levels observed with the different SRI compounds. Discontinuation of the offending medication is usually sufficient to eliminate clinical and biological signs. Currently, the information provided to healthcare practitioners about the risk of hyperprolactinaemia associated with SRI therapy is insufficient. The risk of occurrence of hyperprolactinaemia (with or without clinical signs) should be explicitly mentioned in the labelling of all SRI molecules. Further studies are warranted to evaluate the true risk of hyperprolactinaemia with the individual compounds of this pharmacological class.

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