

Research Article

Antipsychotics and Hyperprolactinemia: Prevalence and Risk Factors

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Abstract

Hyperprolactinemia, a largely underestimated frequent endocrine disorder, may be due to various causes including different treatments. Antipsychotics, particularly, play a major role in its occurrence. Our Objectives are to estimate the prevalence of hyperprolactinemia among patients treated with a single antipsychotic and to specify the risk factors for its occurrence.

It's a cross-sectional study over a 6-month period realized at the Psychiatry Department of Mahdia Hospital, Tunisia on outpatients treated with a single antipsychotic on stable doses for 12 weeks and fulfilling the inclusion and exclusion criteria. A dosage of plasma prolactin levels was carried out then confirmed by a second dosage in case of abnormal levels in the first one. A Magnetic Resonance Imaging (MRI) of the pituitary gland was performed for patients with prolactin levels higher than 150ng/ml.

The study of 92 patient's files, the prevalence showed that of patients had hyperprolactinemia 34.8% and 7.6% had prolactin levels higher than 150ng/ml. An MRI of the pituitary gland was performed for these latter which revealed 2 cases of macro adenoma. The analytic study concluded that 7 factors were significantly correlated with hyperprolactinemia. These factors were as follow : gender female ; consumption of psychoactive substances; side effects of antipsychotic; prescription of atypical antipsychotic; the nature of the prescribed antipsychotic: Haloperidol/ Amisulpride, an antipsychotic dose higher than equivalent 1000 mg of chlorpromazine and the association of psychotropic drugs.

Antipsychotics induced hyperprolactinemia has not been adequately evaluated and despite its frequency, and clinical consequences such as sexual disorders.

INTRODUCTION

Prolactin (PRL) is a hormone, mainly secreted by lactotroph cells of the anterior pituitary gland. Recent studies have shown it may also be produced by many extra pituitary cells [1]. Hyperprolactinemia is a disorder of the hypothalamic-pituitary axis which can be caused by several mechanisms [2]. Hyperprolactinemia, a largely underestimated frequent endocrine disorder, may be due to various causes including different treatments. Typical antipsychotic agents are more likely to cause hyperprolactinemia than atypical antipsychotic agents. The frequency of clinical symptoms is often correlated to the increase in prolactin level; however, hyperprolactinemia can be asymptomatic. The most frequent symptoms of chronic hyperprolactinémie include reproductive dysfunction, sexual impairment, breast pathology, abnormalities associated with

chronic hypogonadism, behavioral and mood alterations, possible immunologic depression [3]. These symptoms are not always reported by the patients, which hinders any accurate assessment of hyperprolactinemia prevalence.

OBJECTIVES

To estimate the prevalence of hyperprolactinemia among patients treated with a single antipsychotic.

To precise the risk factors for hyperprolactinemia occurrence according to the antipsychotic prescribed.

METHODOLOGY

It is a cross-sectional study over a 6-month period, from January 2nd, 2014 to June 30th 2014, realized in the Psychiatric Department of Mahdia Hospital, Tunisia, on outpatients followed

and treated with a single antipsychotic and fulfilling the inclusion and exclusion criteria.

Inclusion criteria

Prescription of a single antipsychotic; Duration of prescription longer than 12 weeks on stable doses; Two Dosages of prolactin levels; A normal thyroid function and informed consent of the patient.

Exclusion criteria

Prescription of two antipsychotics or more; Prescription of SSRIs antidepressants or MAO inhibitors; Prescription of dopamine antagonist, oestrogenics, opioids or a central antihypertensive; pregnancy or breastfeeding; Primary hypothyroidism; Ovarian tumors or a polycystic ovarian syndrome and renal failure or hepatic insufficiency.

Data collection

Data were collected from patients and medical records, using a preset sheet including 25 items that explore the sociodemographic, clinical, therapeutic and evolutionary characteristics of the disorder (type and class of the antipsychotic prescribed, duration of treatment, equivalent dosage in chlorpromazine, prescription of another psychotropic treatment and presence of sexual and endocrine side effects).

Determination of prolactin levels:

Laboratory tests including a plasma prolactin test and a thyroid function test were requested for all patients at 08 am and methods supported by electrochemiluminescence (instrument Roche Diagnostics, Cobas e 411 analyzer/2008/Japan). The control of prolactin levels was asked in case of anomaly objectified in the first dosage. All assays were performed in the laboratory of the Hospital Mahdia, Tunisia under the standard rules of sampling (fast, on an empty stomach, in the morning and cautious).

Detection of microadenomas by a pituitary magnetic resonance imaging (MRI) of patients with high prolactin level (150 ng/ml) was performed with a GE 1.5 Tesla machine and using a standard imaging protocol:

- Precontrast T1 weighted thin slices (sagittal and coronal plans).
- Coronal T2 slices.
- Coronal T1 slices with dynamic gadolinium.

Statistical analysis

The data were entered into a computer software compatible with Excel, and statistical analyzes were performed using SPSS 18.0 for Windows. We calculated simple frequencies and relative frequencies (percentages) for categorical variables, means and standard deviations (SDs) determining the scope (range) for quantitative variables.

In the analytical study, hyperprolactinemia was the subject of a bivariate analysis by crossing with 22 variables : age, sex, origin, professional situation, socioeconomic level and education, surgical and gynecological history, somatic comorbidity, addiction, psychiatric diagnosis, age at onset of the disorder,

duration of the disorder, number of hospitalization, modality of prescription, antipsychotic class, type of antipsychotic, duration of prescription antipsychotic, dosage, side effects, quality of monitoring and observance; using each time, for statistical comparisons, the Chi-square test. The confidence interval was 95% and the P <0.05 level was considered significant.

RESULTS

Ninety-two patients (92) followed at the psychiatry consultation and fulfilling the criteria of inclusion and exclusion participated in this study.

I- Characteristics of the study population

1- Sociodemographic characteristics: Patient's age ranged from 20 to 78 years with an average of 39 and a standard deviation of 11.87. The study population consisted of 53 men (57.6%) and 39 women (42.4%): a sex ratio (M / F) of 1.36. Patients with single marital status represented 55.4%, followed by married status (40, 2%). 47.8% were unemployed. Twenty patients were pre-menopausal, 13 in peri-menopause and 6 in post-menopause (Table 1).

2- Clinical and evolutionary characteristics: Most patients were followed for schizophrenia and other psychotic disorders (63.1%), followed by mood disorders (33.6%). **Age at onset of the disorder** ranged from 19 to 68 years with an average of 24.4 years and a standard deviation of 7.57. **Duration of the disorder** ranged from 1 to 44 years with an average of 14.9 years and a standard deviation of 8.91. Eleven patients were followed for somatic disease (12%). 6 patients had diabetes, 4 patients had essential hypertension, and one patient was followed for gout. All these patients were taking treatments other than psychotropic drugs. The use of psychoactive substances was observed in 42.4% of patients. Tobacco, alcohol and cannabis were the most consumed substances with respective rates of 49, 27 and 12.5% (Table 1).

Table 1: Characteristics of the study population.	
Sociodemographica characteristics	A±SD* ou N (%)**
Âge	39±11,87
Men / Women	53 (57,6)/39 (42,4)
Marital Status: single	55.4%
Profession: unemployed	47,8%
Clinical and evolutionary characteristics	
Age at onset of the disorder	24,4±7,57
Duration of the disorder	14,9±8,91
Schizophrenia and other psychotic disorders	63.1%
Somatic disease	12%
Use of psychoactive substances	42,4%
Therapeutic characteristics	
Antipsychotic treatment in monotherapy	27.2%
Atypical antipsychotics	47.8%
Duration of prescription (weeks)	133.5
Equivalent in Chlorpromazine	612.4
Nature of endocrine and sexual side effects	
Secondary amenorrhrea	23.8%
Galactorrhrea	17.5%
Erectile dysfunction	27%
Abbreviations: *A±SD : Average ± Standard-Deviation; **N(%) : Number of patients (%).	

3-Therapeutic characteristics: All patients were under antipsychotic treatment, prescribed in 27.2% of cases alone. Among those on a combination, 25% received a benzodiazepine and 33.7% a mood stabilizer treatment. The prescription of corrective treatment was noted in 14.1% of cases. Nearly half of our study population were treated with atypical antipsychotics (47.8%), 52.2% were treated with conventional antipsychotic. For the latter, Haloperidol ranked first (25%) followed by Chlorpromazine and Fluphenazine at equivalent rates (8.7%). In the group treated with atypical antipsychotics, Amisupiride was the most prescribed (18.5%).

Duration of prescription ranged from 12 to 963 weeks with an average of 133.5 and a standard deviation of 18.57. For 58.7% of patients, the stable dose prescription period was over 50 weeks. Dosage of antipsychotic treatment (Equivalent in Chlorpromazine) ranged from 25 to 4000 mg of chlorpromazine equivalent doses, with an average of 612.4 and a standard deviation of 78.56. For 1/3 patients only, the dosage was less than 250 mg in equivalent of Chlorpromazine. Patients with regular follow-up represented 73.9% of cases. Good adherence to treatment was observed in 66.3% of patients (Table 1).

4 - Nature of endocrine and sexual side effects: Forty-two patients, representing 45.7% of the study sample reported the presence of side effects. For female patients, the most reported side effects were secondary amenorrhea (23.8%) and galactorrhea (17.5%). For men, it was erectile dysfunction (27%) and decreased libido (25.4%) (Table 1, Figure 1).

II- Hyperprolactinemia

1- Prevalence: Plasma prolactin levels ranged from 1.6 to 327.06 ng / ml with an average of 36.84 and a standard deviation of 5.63. Nearly 2/3 of the study population had prolactin levels within normal ranges (Table 2).

After a first assay confirmed by a second assay, the prevalence of hyperprolactinemia was 34.8% (32 patients). Plasma prolactin level was greater than 150 ng / ml in 7.6% of cases (Figure 2).

2- Thyroid function: An assay of TSH performed for the entire study population was normal with levels ranging from 0.73 to 5.14 mUI/l and an average of 2.53 and a standard deviation of 0.11.

3- Magnetic resonance imaging (MRI): A pituitary MRI was performed on the seven patients who had plasma prolactin levels higher than 150 ng/ml confirmed by a second assay. The MRI was normal for 5 patients, however, a micro adenoma for 2 patients (Figure 3) and an osseous lipoma of the clinoid processes were revealed.

For 2 cases of microadenomas, patients were referred to the Endocrinology Department where a specialist's opinion concluded that a prescription of increased doses of Bromocriptine with monitoring of the plasma prolactin levels within three months and surveillance of psychic effects given the risk of psychotic decompensation in dopaminergic therapy.

In the case of osseous lipoma of the clinoid process, the neuro-surgical specialist concluded that it was a rare form of lipoma which requires a simple monitoring given the lack of clinical impact.

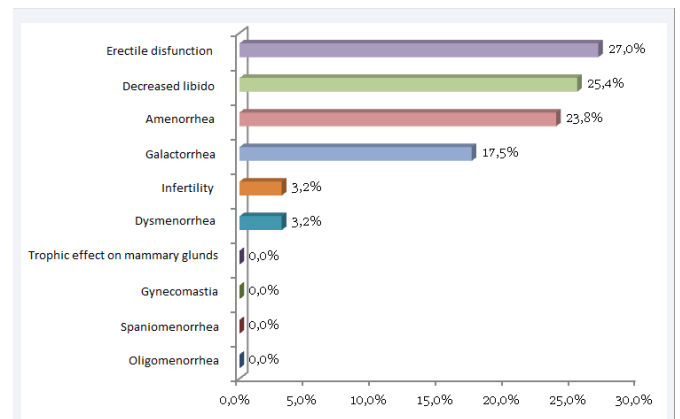


Figure 1 Distribution of patients according to endocrine and sexual side effects.

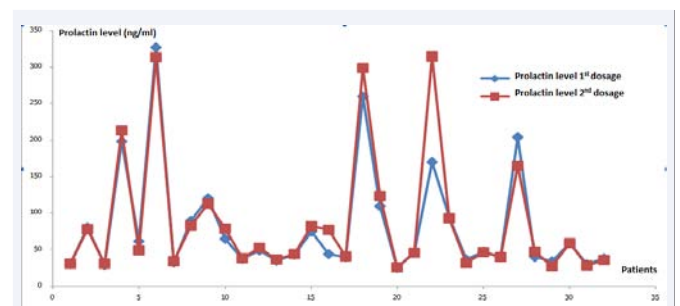


Figure 2 Prolactin level distribution in first and second prolactin dosage.



Figure 3 MRI coronal sequence showing a left microadenoma.

4- Hyperprolactinemia and class of antipsychotics: Plasma prolactin levels greater than 25ng/ml were observed among 23.9% of patients treated with atypical antipsychotics versus 10% among patients treated with classical antipsychotics. Haloperidol was the classical antipsychotic which was the most associated with hyperprolactinemia (5.4%) while patients treated with levomepromazine didn't present this side effect. Hyperprolactinemia was observed among 13% of the patients treated with amisulpride and 5.4% of those treated with risperidone. Aripiprazole didn't lead to any biological abnormalities (Figure 4).

III- Factors associated with hyperprolactinemia

Results showed that only 7 factors among the 22 factors studied were significantly correlated with hyperprolactinemia. These factors were: female gender, use of psychoactive substances, presence of side effects, prescription of atypical antipsychotic, class of antipsychotic: haloperidol/amisulpride, prescribed dose greater than equivalent 1000 mg of chlorpromazine and association of psychotic drugs (Table 3).

DISCUSSION

1- Methodological aspects

Hyperprolactinemia, as a side effect of antipsychotics, has been the subject of several studies worldwide. These studies included its prevalence its associated factors and an evaluation of therapeutic interventions. Lack of data on this subject in Tunisia led us out of the usual nosographic framework focused on the assessment of clinical and evolutionary characteristics and we were rather interested in a common side effect affecting sexual and family life of patients followed in psychiatry.

Table 2: Distribution of patients according to plasma levels of prolactin.

Plasma prolactin level (ng/ml)	Number	Frequency (%)
<25	60	65.2
25-50	18	19.6
51-150	7	7.6
>150	7	7.6
Total	92	100

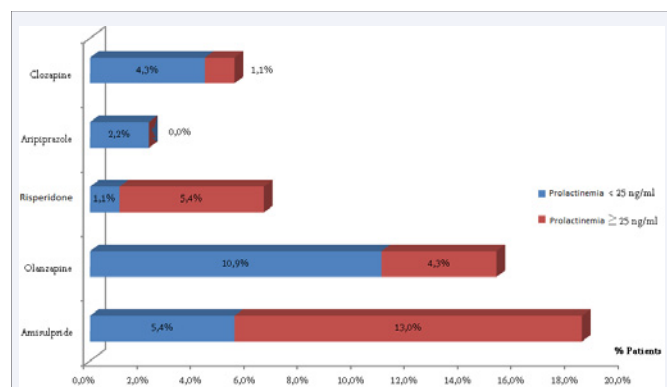


Figure 4 Distribution of patients with hyperprolactinemia according to the class of atypical antipsychotic.

Table 3: Factors were significantly correlated with hyperprolactinémie.

Factoresa	p
Gender female	0,004
Consumption of psychoactive substances	0,04
Side effects of antipsychotic	<10 ⁻⁴
Prescription of atypical antipsychotic	0,003
Nature of the prescribed antipsychotic : Haloperidol/Amisulpride	0,008/0,01
Antipsychotic dose higher than equivalent 1000 mg of chlorpromazine	0,04
Association of psychotropic drugs	0,04

Regarding the inclusion criteria, the prescription of a single antipsychotic was required in our study to ensure the accountability of each treatment in the appearance of a possible hyperprolactinemia. This criterion adopted by several authors is justified by the variable potential of antipsychotics in causing hyperprolactinemia, involving complex mechanisms. Therefore, the antipsychotic leading to this side effect must be identified before starting any treatment [4]. Concerning the prescription duration of the antipsychotic on stable doses, we complied with the literature data on the increase of the basal rate and stabilization of prolactin levels among patients treated with antipsychotics. As for confirmation of a first high dosage of prolactin by a second one, it's a desirable measure in order to confirm the diagnosis [5, 6].

Regarding the exclusion criteria, we chose to eliminate other causes of hyperprolactinemia in particular physiological causes (pregnancy and lactation), pathological causes (tumor lesions of the hypothalamic-pituitary axis, primary hypothyroidism, polycystic ovaries and chronic kidney and liver failure) and other iatrogenic causes (SSRIs, antiemetics, estrogen and central antihypertensives) [7-9]. One limitation of our study is that the normal range for basal TSH is too broad. Some authors recommend classify patients into 2 groups (Low normal (≤ 2.5 mUI/L) and High normal (≥ 2.5 mUI/L) TSH groups) [10].

Concerning pituitary MRI, we followed the instructions and new proposals of an international group of experts in psychiatry, endocrinology, toxicology and pharmacology [11] if prolactin levels exceed 150ng/ml to detect a prolactinoma.

2- Results

Prevalence of hyperprolactinemia: Hyperprolactinemia is most likely underestimated and undiagnosed [12, 13]. It is almost always symptomatic but clinical signs are not always put forward by patients. Therefore, only patients for whom overt clinical signs are mentioned are subject to a dosage of prolactin [14]. An English study on 178 patients treated with antipsychotics showed prevalence close to ours (33%), men in 17.6% of cases and women in 47.3% [15]. Other studies confirm that hyperprolactinemia is more common among women than men [16], this result was also found in our study (12 vs 20, $p=0,004$).

It also appears that premenopausal women are more subject to hyperprolactinemia than in postmenopausal period. This result was observed in our study (4 vs 2, $p=NS$). The frequency coincides with frequency among men [16].

Hyperprolactinemia and antipsychotics: Antipsychotics are the most involved pharmacological class in the occurrence of hyperprolactinemia.

This endocrine disorder is an important therapeutic problem given that psychiatric disorders often require a long-term treatment with antipsychotics.

Antipsychotics act by blocking dopamine D2 receptors, this mechanism is responsible not only for their therapeutic effects but also for their side effects. Dopamine exerts, in fact, a negative control on prolactin synthesis and secretion by binding to D2 receptors on lactotrophs in the anterior pituitary. Antipsychotics, inhibiting this binding, induce a lifting of the inhibition of dopamine which can no longer bind to its receptors. Thus, the

mechanism of hyperprolactinemia caused by antipsychotics occurs indirectly.

It seems that occurrence of antipsychotics-induced hyperprolactinemia is related to their ability to bind and antagonize the D2 receptors in the pituitary level [12]. Specifically, it seems that all antipsychotics cause an increase in prolactin which depends quantitatively on the molecules administered [17]. The faster the antipsychotic dissociates from D2 receptor, the lower the effect on prolactinemia, however, there has to be a sufficient duration of binding to induce a therapeutic effect [18]. It should be noted that the connection of an antipsychotic to the D2 receptor varies both according to the half-life and its affinity for this receptor. Kapur et al. have shown that the ability of the atypical antipsychotics to cross the blood-brain barrier had an impact [18]. It appears that the antipsychotics crossing the least that barrier, that is, those for which the occupancy rate of pituitary receptors is higher than the central receptors are amisulpride and risperidone [18]. These are the antipsychotics which cause the most hyperprolactinemia. The higher the ratio is in favor of pituitary receptors, the more occurs hyperprolactinemia. These findings are similar to our results showing involvement of atypical antipsychotics in the occurrence of hyperprolactinemia.

Finally, it appears that hyperprolactinemia increases as the dose of antipsychotics used increases, at least for classical antipsychotics [19,20]. Our study also found that the risk of hyperprolactinemia was associated with antipsychotic doses higher than 1000 mg equivalent chlorpromazine doses. However, low doses of antipsychotics can cause significant hyperprolactinemia. Therefore antipsychotics can be classified into two categories depending on their potential to cause hyperprolactinemia [17, 21]. Any classical antipsychotics have a high potential of causing hyperprolactinemia. Conversely, the risk of hyperprolactinemia caused by atypical antipsychotics varies depending on the active substance used. Thus, amisulpride and risperidone have a strong potential to cause hyperprolactinemia while Clozapine, Olanzapine and the Aripiprazole have the least potential [4].

Hyperprolactinemia and classical antipsychotics: In our study we found a prevalence of 10.9% among patients treated with classical antipsychotics in which haloperidol ranked first (5.4%). In study carried out reports a on 15 patients treated with haloperidol Madhusoodanan et al. observed a fast increase in prolactin during the first 6-9 days and then a stabilization of the baseline level below 77 ng / ml for any dose administrated [6]. With Fluphenazine, Goodnick et al. showed an increase in two phases: a first phase during the first three days followed by a second phase in the following weeks [22].

In general, a prolactin level among patients treated with classical antipsychotics increase few hours after starting the treatment and continues throughout its duration. A mean duration of treatment (three to nine weeks), according to Meltzer et al., may cause an increase in basal prolactin levels of a factor of 10 [23]. Among patients who receive a long-term treatment, we sometimes observe instead a partial tolerance with a rate that is close to normal, but still higher in most cases [24]. At the end of treatment, normalization takes place in two to three weeks and in about 6 months in cases of intramuscular deposit [21].

Hyperprolactinemia and atypical antipsychotics: Through our results, we observed a hyperprolactinemia prevalence of 23.9% among patients treated with atypical antipsychotics including amisulpride (13%) followed by risperidone (5.4%), while a low rate was found with clozapine (1.1%) and no cases with aripiprazole.

These differences are explained by the mechanism of action of each antipsychotic. While classical antipsychotics have a complete antagonist activity on D2 receptors, some atypical antipsychotics such aripiprazole have an agonist/antagonist activity which enables the dissociation of the receptor, normalizes the tuberoinfundibular dopaminergic function and limits the increase of prolactin levels [25].

This partial agonist property to D2 and also 5-HT1A and antagonist property to 5-HT2A allows a decrease of prolactin levels [25]. The another theory suggests that the simultaneous binding of D2 and 5-HT1A receptors restores balance between dopamine and serotonin function which approximates physiological conditions [4].

Olanzapine has, for its part, more affinity for the 5-HT2 receptor than for the D2 receptors, regardless of the dose administered. However, the higher the administered dose is, the higher the occupancy of D2 receptors. From a dose of 30 mg daily, occupancy exceeds 80% and clinical signs of hyperprolactinemia appear [6].

Moreover, Clozapine interacts selectively with D1 more than with D2 receptors, histamine receptors and 5-HT2 receptors. Thus, it changes the functioning of dopaminergic neurons in pre- and postsynaptic levels [6].

The absence of side effects such as hyperprolactinemia among patients treated with Clozapine is due to the direct action of the active substance on tuberoinfundibular neurons [26]. In fact there is a very fleeting increase of prolactin levels followed by a rapid return to basal rates. At high doses, Clozapine inhibit directly the release of prolactin.

Melkersson evaluated the incidence of hyperprolactinemia among 75 patients treated with Risperidone, Olanzapine and Clozapine [27] and found affects 89% of patients receiving risperidone (3mg/day), 24% of patients treated by Olanzapine (10mg/day) and 0% of patients treated with Clozapine (400mg/day). Symptoms as menstrual cycle disorders, galactorrhea, sexual impotence, oligospermia or low libido are also more common in patients receiving risperidone (44%) vs 3% with Olanzapine and 0% with Clozapine)

Finally, Amisulpride is an atypical antipsychotic which has a high potential to induce hyperprolactinemia. It causes hyperprolactinemia comparable to those observed with classical antipsychotics as observed in the study of Frix and Laux [28]. It seems that this side effect is caused by a low passage of the blood-brain barrier resulting in a high occupancy of D2 and D3 receptors in the pituitary level compared to the central level.

Hyperprolactinemia appears during acute treatment and persists when treatment is extended. However a dose-response relationship doesn't seem to exist [28].

Hyperprolactinemia and adenoma: Our study revealed

2 cases of pituitary adenoma with prolactin levels higher than 300 ng / ml. Pelever et al. [11] reported that this risk increases if prolactin level is higher or equal to 150 ng / ml. It has to be noted that treatment of hyperprolactinemia by a dopamine agonist should be restricted for exceptional cases because of the risk of worsening of the psychiatric pathology [7-9, 11].

CONCLUSION

Antipsychotics induced hyperprolactinemia has not been adequately evaluated and despite its frequency, and clinical consequences such as sexual disorders. Moreover, there long term risks such as bony abnormalities and possible increase of the risk of breast or prostate cancer. For all these reasons, further studies should be carried out through a pre-therapeutic assessment of patients as a part of the risk-benefit balance of a treatment based on antipsychotics.

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