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Literature Review

Hyperprolactinemia as a side effect of using antipsychotics In Schizophrenic Patients

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Abstracts

Introductions: Antipsychotics are still the mainstay of schizophrenia management. Antipsychotics are antagonistic to postsynaptic dopamine receptors in the brain. Blockade of dopamine receptors in the tuberoinfundibular pathway by antipsychotics will cause the side effect of hyperprolactinemia. **Objectives:** This review describes hyperprolactinemia induced by antipsychotic use and its clinical effects, monitoring, and management. Methods: reference search through Google Scholar with keywords schizophrenia, antipsychotics, prolactin, hyperprolactinemia, clinical effects of hyperprolactinemia, diagnosis of hyperprolactinemia, monitoring of hyperprolactinemia, management of hyperprolactinemia. **Results:** Clinicians need to take a diagnostic approach to identify the etiology of hyperprolactinemia, monitor the clinical symptoms of hyperprolactinemia during the administration of antipsychotics, and immediately carry out management according to existing strategies by considering some general principles and considerations. **Conclusions:** Schizophrenia is a severe mental disorder that lasts long, requiring long-term and continuous therapy. Administration of antipsychotics is still a mainstay in the management of schizophrenia. Antipsychotics are antagonists to postsynaptic dopamine receptors in the brain. The antipsychotic effect of blocking dopamine receptors not only improves the symptoms of schizophrenia but also causes side effects. The side effect when the tuberoinfundibular dopamine pathway is blocked is an increase in prolactin levels called hyperprolactinemia.

Keywords: Schizophrenia, Antipsychotics, Hyperprolactinemia, Antipsychotic Side Effects, Management Of Hyperprolactinemia

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Introductions

Schizophrenia is one of the most common forms of severe mental disorder, manifesting as severe and persistent psychotic symptoms accompanied by various cognitive dysfunctions and prominent psychosocial disturbances. This disorder lasts long and makes the patient suffer a lot throughout life, requiring long-term and continuous therapy [1].

A complex interaction between biological, genetic, and environmental factors causes schizophrenia. Consequently, patients affected by this disorder must receive integrated care that includes medication and psychosocial therapy, physical health care, and treatment of comorbidities [2].

Antipsychotic drugs are still a mainstay in the management of schizophrenia. About 70% of patients treated with antipsychotics achieve remission or improvement. However, patients can experience side effects from antipsychotic administration, including hyperprolactinemia [1].

A study showed that drug-induced was the most common cause (45.9%) of the total cases of hyperprolactinemia [3]. The incidence of hyperprolactinemia on treatment with dopamine antagonists for women was 8.7 per 100,000 person-years, while for men, it was 1.4 per 100,000 person-years. Incidents as high as 70% have been reported with antipsychotic use [4]. In drug-induced hyperprolactinemia, morbidity and mortality are increased due to an increased risk of diabetes, cardiovascular disease, fractures, and infectious diseases [5]. Hyperprolactinemia plays a role in stopping antipsychotic treatment by patients, so it must be managed properly [6].

Antipsychotics

Antipsychotics are antagonists to postsynaptic dopamine receptors in the brain. Antipsychotics are categorized into two main groups: typical antipsychotics or First Generation Antipsychotics (FGA) and atypical antipsychotics or Second Generation Antipsychotics (SGA). Typical antipsychotics work by blocking dopamine D2 receptors in all dopamine pathways (mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular). Blockade of dopamine receptors in the tuberoinfundibular pathway can cause an increase in prolactin levels or hyperprolactinemia. At the same time, atypical antipsychotics have additional properties of serotonin 5HT2A receptor antagonists and partial 5HT1A receptor agonists or partial agonists of dopamine D2 receptors. This makes atypical antipsychotics similar in clinical effect to typical antipsychotics but with fewer side effects of hyperprolactinemia [7].

Physiology of Prolactin

Prolactin is primarily synthesized and secreted by lactotrophic cells of the anterior lobe of the pituitary gland (adenohypophysis), with the deeper zones more responsive to dopamine. In contrast, the outer zones are more responsive to Thyroid-Releasing Hormone (TRH). Prolactin secretion is under complex control of peptide and steroid hormones and neurotransmitters, which act as inhibitory or stimulatory factors. Prolactin inhibitory factors include dopamine, gamma-aminobutyric acid (GABA), somatostatin, acetylcholine, norepinephrine, and growth hormone (GH). Meanwhile, prolactin-stimulating factors include angiotensin II, estrogen, thyrotropin-releasing hormone (TRH), endogenous opioids, vasopressin, and galanin [8].

Hyperprolactinemia

Hyperprolactinemia increases serum prolactin levels that persist above normal limits under physiological conditions. Hyperprolactinemia is defined as prolactin levels above 20 ng/ml in men and 25 ng/ml in women in a fasted state for at least 2 hours after waking [8].

The division of degrees of hyperprolactinemia, according to Serri, uses ng/ml units, namely mild hyperprolactinemia with levels of 31-50 ng/ml, moderate hyperprolactinemia with levels of 51-75 ng/ml, and severe hyperprolactinemia with levels> 100 ng/ml [9]. Another unit used is mIU/L; according

to WHO standards, one ng/ml equals 21.2 mIU/L. Peveler uses the mIU/L unit, stating that mild hyperprolactinemia with levels <1000 mIU/L, moderate hyperprolactinemia with levels of 1000-2000 mIU/L, and severe hyperprolactinemia with levels >2000 mIU/L [10].

The degree of hyperprolactinemia can be related to the clinical symptoms experienced. Mild hyperprolactinemia is associated with decreased libido and infertility. Moderate hyperprolactinemia is associated with oligomenorrhea. Meanwhile, severe hyperprolactinemia is associated with amenorrhea, galactorrhea, and hypogonadism [9].

The causes of hyperprolactinemia can be categorized into physiological causes, pharmacological causes, and pathological causes. Physiological causes include endogenous estrogens, lactation, stress, and physical exercise. Pharmacological causes include antipsychotics, antidepressants, antiemetics/prokinetics, opioids, and antihypertensives (such as verapamil, methyldopa, and reserpine) [11]. Pathological causes include disorders of the pituitary gland and hypothalamus, endocrine or systemic conditions (such as hypothyroidism, primary adrenal insufficiency, polycystic ovarian syndrome (PCOS), chronic kidney disease, and cirrhosis), neurogenic hyperprolactinemia (such as traumatic lesions and irritable chest wall disorders), and idiopathic hyperprolactinemia [12].

Dopamine, Antipsychotics and Hyperprolactinemia

Dopamine is the most critical prolactin-inhibiting factor. Dopamine binds to D2 dopamine receptors on lactotroph cell membranes and inhibits prolactin gene transcription, prolactin synthesis and release, and lactotroph proliferation. Blockade of D2 dopamine receptors affects prolactin secretion. Inhibition of dopamine transmission primarily through blockade of dopamine D2 receptors on lactotroph cells results in disinhibition of prolactin secretion. Antipsychotics have a dopamine D2 receptor blockade effect and, therefore, can increase prolactin secretion. The stronger the dopamine blockade, the higher the prolactin level [8].

Antipsychotics are also grouped into prolactin-rising (FGA and some SGAs including Amisulpride, Risperidone, and Paliperidone) and prolactin-sparing (some SGAs including Clozapine, Quetipepine, Olanzapine, Ziprasidone and Aripiprazole) [8]. This is based on variations in the speed of dissociation of D2 dopamine receptors, the ability to cross the blood-brain barrier, the presence of D2 dopamine receptor polymorphisms, and the degree of serotonergic inhibition [11]. Prolactin-sparing is an antipsychotic that may cause a slight or transient increase in prolactin levels within the upper limits of routine and a lower frequency of side effects associated with hyperprolactinemia [13].

Amisulpride is considered to have the greatest potential to cause hyperprolactinemia of all antipsychotic classes. These effects occur dose-independently and resolve quickly after drug discontinuation [11]. Hyperprolactinemia is rarely seen in patients treated with aripiprazole because it is a partial dopamine agonist and can often reverse hyperprolactinemia induced by other antipsychotics [6,12].

Hyperprolactinemia clinical effects

Some of the clinical effects of hyperprolactinemia are as follows:

1. Effects on reproduction

In women, menstrual disorders (amenorrhoea or oligomenorrhea), infertility, decreased libido, and galactorrhea occur. Postmenopausal women may develop symptoms of vaginal dryness, dyspareunia, and loss of libido. In men, there is a decrease in libido, erectile dysfunction, reduced testosterone, and impaired spermatogenesis that causes infertility [4, 11].

The literature states that the prolactin concentration can increase up to 10 times the average level in women. In contrast, on antipsychotic therapy, 75% or more of women

have amenorrhea with or without galactorrhea in several studies [14].

2. Effects on bones

The direct mechanism on bone is the presence of prolactin receptors on osteoblasts, which have been shown to reduce the number of osteoblasts, causing decreased bone proliferation and density [15]. The indirect mechanism through the hypothalamic-pituitary-gonadal axis using suppression of gonadal hormone levels causes abnormal bone metabolism and an increase in osteoclast activity, which is not compensated by an increase in osteoblast activity [15–17].

Mild hyperprolactinemia causes greater bone resorption than bone formation, and severe hyperprolactinemia stimulates bone resorption and inhibits bone formation, resulting in bone microdamage [18].

3. The risk of developing breast cancer

Antipsychotics, which induce hyperprolactinemia, trigger precancerous cells to develop into cancer cells through Janus Kinase 2 (JAK2) and Signal Transducer and Activator of Transcription 5 (STAT5) [19].

4. Other side effects

Hyperprolactinemia is associated with an increased risk of prostate cancer, venous thromboembolism, reduced glucose tolerance, hyperinsulinemia, and changes in behavior and mood. However, it still requires more data [20].

Hyperprolactinemia in patients experiencing first-time psychotic episodes

Several studies have shown that hyperprolactinemia can occur in patients who experience their first psychotic episode even before receiving antipsychotic therapy [21,22]. The implication in clinical practice is that it is necessary to know the prolactin level before the patient receives antipsychotic therapy to ensure that hyperprolactinemia is not a pre-existing condition. It is also important for choosing an antipsychotic or switching to another antipsychotic [8,23].

Diagnosis Approach

To identify the etiology of hyperprolactinemia, several things must be taken into account, namely: medical history (such as symptoms, use of substances that can increase prolactin levels, excessive breast stimulation), physical examination (e.g., galactorrhea, gynecomastia, goiter, spider angioma, ascites, edema, wall lesions chest, nipple piercings), laboratory results (thyroid, liver, and kidney function tests, pregnancy tests), to radiological results (MRI) [4,12].

Monitoring

When antipsychotics are administered, the prolactin level should be rechecked three months after administration unless the patient develops symptoms of hyperprolactinemia before three months; then, the test should be repeated immediately. If a mild to moderate increase in prolactin levels is found or if there is doubt about the cause (whether it is due to antipsychotics or other conditions), then the examination should be repeated, paying attention to whether the symptoms of hyperprolactinemia appear. However, suppose a single blood test shows a very high prolactin level (> 2000 mIU/L or the equivalent > 95 ng/ml) or a high prolactin level with supporting symptoms. In that case, confirming hyperprolactinemia and being treated is sufficient [20].

Management

Hyperprolactinemia management aims to normalize prolactin levels, restore gonadal dysfunction (menstrual and sexual problems), and prevent osteopenia and osteoporosis [11,20]. Several strategies can be taken in managing hyperprolactinemia caused by antipsychotics:

1. Reducing the dose of antipsychotics

This is a simple and reasonable choice of action, but it is necessary to consider the risk of recurrence in psychotic patients [20,24].

2. Switch to a prolactin-sparing antipsychotic

Several studies reported significant improvements in hyperprolactinemia symp-

toms with normalization of prolactin levels. If this option is taken, then an antipsychotic switch is applied gradually and is preferable to cross-tapering or overlapping rather than an instantaneous switch [20,24,25].

3. Addition of Aripiprazole

In a meta-analysis by Li et al. in 2013, it was found that adding aripiprazole at a dose of only 5 mg/day was associated with normalization of prolactin levels by 79% [20,24]. Adding aripiprazole causes polypharmacotherapy, which may increase the risk of certain side effects such as extrapyramidal symptoms, diabetes, or antipsychotic-induced metabolic syndrome [24,25].

4. Addition of dopaminergic drugs

This is controversial because it can worsen psychotic symptoms. So, this option is only used if the previous strategy (use of aripiprazole) was ineffective or if there is a pituitary adenoma [20,24].

5. Other additional therapy

These include hormonal therapy in patients with long-term hypogonadism and or osteoporosis [20], administration of metformin [26,27], and administration of Pheony-Glicyrrhiza [28,29].

6. Refer to endocrinologist

If the etiology of hyperprolactinemia is unclear, prolactin levels continue to rise despite intervention, hyperprolactinemia with prolactin levels > 3000 mIU / L equivalent to > 141 ng/ml, or suspected or confirmed pituitary adenoma [20].

Some general principles for risk reduction and management of hyperprolactinemia in patients stabilized with antipsychotic treatment [30]:

1. Check the baseline prolactin level when starting an antipsychotic.
2. Explore sexual history (and menstrual history in women) when starting antipsychotics for comparison with subsequent clinical symptoms.
3. Assess and document the response of psychiatric illness to antipsychotics to facilitate decision-making based on the effectiveness of antipsychotics compared to the risk of prolactin elevation and potential side effects of the drugs prescribed.
4. Involve the endocrinologist if the prolactin level is> 100 ng/ml or 2120 mIU / L and if starting hormone therapy for hyperprolactinemia
5. Prolactin-raising drugs are used cautiously in patients under 25 years of age, women of childbearing age, women planning pregnancy, patients with osteoporosis, and patients with a history of hormone-dependent breast cancer.
6. Testosterone levels in men should be checked when hyperprolactinemia is identified because maintaining testosterone levels within a normal range is essential for bone health.
7. Take a collaborative approach to treatment decision-making, provide information to patients, and discuss the benefits of treatment and possible side effects, both short and long-term, associated with hyperprolactinemia.
8. Involve the patient in making lifestyle changes to reduce the risk of side effects associated with hyperprolactinemia, including smoking, inactivity, vitamin D deficiency, and alcohol consumption, contributing to osteoporosis.

Several points of consideration in the management of hyperprolactinemia induced by antipsychotics are [30]:

1. Regular monitoring of serum prolactin levels should be performed in asymptomatic cases to assess response to intervention.
2. It does not support stopping antipsychotics to determine whether they affect accurate prolactin levels, even though the initial information is unknown because psychotic symptoms are at risk for exacerbations and relapse.
3. Substitute antipsychotics to reduce prolactin levels should be undertaken with extreme caution when the patient is mentally stable, only when clinical symptoms of hyperprolactinemia occur, and when other options for

intervention are unsuccessful.
4. Does not support the administration of dopamine agonists for the treatment of hyperprolactinemia in patients whose psychotic symptoms worsen as a result of this action until there is an explanation of its efficacy and risk.
5. Premenopausal women with antipsychotic-induced hyperprolactinemia may benefit from the combined oral contraceptive pill (OCP) intervention, which helps continue menstruation. Still, it should be noted that OCPs are also associated with the side effects of depression.
6. Refer to an expert if hormone treatment is considered for postmenopausal female patients with antipsychotic-induced hyperprolactinemia.
7. Selective estrogen receptor modulator (SERM) such as raloxifene hydrochloride is approved for use in preventing and treating osteoporosis in postmenopausal women. However, its safety and efficacy for osteoporosis due to hyperprolactinemia remain to be evaluated in clinical trials.
8. Educating patients on preventing unwanted pregnancy when intervention goals are achieved (i.e., prolactin level normalizes) is essential, which can restore fertility.
9. Prolactin level needs to be normalized, and cross-titration to an antipsychotic with evidence of safety in pregnancy is recommended when pregnancy is planned.
10. A collaborative approach to treatment decision-making is recommended, including discussion of medication benefits versus potential short-term and longer-term side effects.

Conclusions

Schizophrenia is a severe mental disorder that lasts long, requiring long-term and continuous therapy. Administration of antipsychotics is still a mainstay in the management of schizophrenia. Antipsychotics are antagonists to postsynaptic dopamine receptors in the brain. The antipsychotic effect of blocking dopamine receptors not only improves the symptoms of schizophrenia but also causes side effects. The side effect when the tuberoinfundibular dopamine pathway is blocked is an increase in prolactin levels called hyperprolactinemia.
Hyperprolactinemia causes clinical effects in the form of reproductive disorders in patients with decreased bone density (risk of osteoporosis). It is also associated with a potential risk of breast cancer and other side effects, requiring more data. Hyperprolactinemia can also be found in patients who experience a psychotic episode for the first time, even though they have not received antipsychotic therapy. Therefore, knowing the initial prolactin level before starting treatment is necessary to ensure no previous hyperprolactinemia.
Clinicians need to take a diagnostic approach to identify the etiology of hyperprolactinemia. Clinicians also need to increase awareness by considering the selection of antipsychotics and monitoring clinical symptoms during antipsychotic administration to minimize these side effects of hyperprolactinemia. Several strategies for managing antipsychotic-induced hyperprolactinemia have been proposed by taking into account some general principles and considerations by involving patients in joint decision-making.

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