DRUG INDUCED HYPERPROLACTINEMIA

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ABSTRACT

Hyperprolactinemia is one of commonest endocrine abnormalities. It can occur due to various reasons and drugs are one of the commonest reasons. Identifying drugs as the potential cause of elevated prolactin and differentiate it from other possible causes are important in clinical practice. It is important to understand the different classes of drugs that could influence the prolactin release and the potency and the pattern of prolactin elevation with each drug class, to formulate a plan of management for these patients. In the update, we have discussed the types of drugs, their relative potencies of causing hyperprolactinaemia and the steps of management of this clinical entity.

Running title: drug induced hyperprolactinemia

Keywords: Hyperprolactinemia, drug induced, antipsychotics.

INTRODUCTION

Hyperprolactinemia is a condition with elevated prolactin levels in the blood, which may be of physiological, pathological or idiopathic origin. It essentially occurs due to pathological or pharmacological disruption of the hypothalamo-pituitary dopaminergic pathways. It is one of the commonest endocrine disorders, mostly affecting females. The prevalence of hyperprolactinemia ranges from 0.4% in an unselected adult population to as high as 9 – 17% in women of reproductive age (1). Galactorrhoea and hypogonadotrophic hypogonadism are the usual clinical consequence of hyperprolactinaemia and therefore, females usually present with galactorrhoea and menstrual irregularities such as oligomenorrhoea or amenorrhoea, while males experience erectile dysfunction. Both sexes may experience loss of libido and infertility.

PHYSIOLOGY

Prolactin (PRL) is a polypeptide with 199 amino acids, which is secreted from the lactotrophic cells of the anterior pituitary. Prolactin is secreted in a pulsatile manner with highest levels occurring during sleep and lowest occurring between 10 a.m to noon. The secreted prolactin gets circulated in different forms, the monomeric (little PRL) with a size of 23kd,

dimeric (big PRL) where the size range from 48 – 56 kd and polymeric forms (big, big PRL) where the size is larger than 1000kd and monomeric form of prolactin is the most active form. Prolactin is mainly responsible for the milk production during pregnancy and lactation (2). Unlike other trophic hormones of the anterior pituitary, prolactin secretion is not regulated by a negative feedback from the peripheral hormones. Dopamine acts as the primary inhibitory factor for prolactin secretion. Dopamine that gets released from the hypothalamus reaches the anterior pituitary via the hypothalamic-pituitary-portal system and inhibits prolactin secretion by binding to the D2 receptors. Numerous other factors such as fibroblast growth factor, epidermal growth factor, vasoactive intestinal polypeptide (VIP), hypothalamic prolactin releasing peptide (PrRP) and oxytocin also can stimulate the synthesis and release of prolactin. Oestrogen has the ability to stimulate the prolactin gene transcription. In addition to these, serotonin opiates and histamine can also have stimulatory effects on prolactin secretion.

Hyperprolactinemia

The prolactin levels are maintained less than 25ug/l in women and less than 20ug/l in men. However, elevated prolactin levels can be seen in certain physiological conditions. Pregnancy is the commonest physiological condition with hyperprolactinaemia where the levels can go up as high as 10-fold from the

baseline. Exercise, meals and chest wall stimulation can also lead to elevated prolactin levels. Although physical and psychological stress can increase prolactin levels, it rarely exceeds 40ug/dl (3).

Prolactinomas account for 25 – 30% of functioning pituitary tumours. Lesions affecting the hypothalamus and the tumours with compression on pituitary stalk such as non-functioning adenomas, gliomas and craniopharyngiomas can also result in prolactin elevation (4). Mild elevation of prolactin is seen in hypothyroidism due to the stimulatory effect of thyrotrophin releasing hormone on prolactin release (5). Due to the impairment renal clearance, elevated prolactin levels can also be seen in chronic renal failure (6).

Drug-induced hyperprolactinemia

There are several drug classes that can influence the prolactin release leading to hyperprolactinemia and the drugs that influence the action of central nervous system dopamine level and the activity is mainly responsible. It is important to differentiate this cause from pathological causes such as prolactinomas.

Antipsychotic Medication

Anti-psychotic drugs are one of the commonest causes of drug-induced hyperprolactinemia (7). Dopamine antagonist effects of these drugs on D2 receptors of the infundibular hypothalamic pathways and the lactotrophs are mainly responsible for the hyperprolactinaemia. A study done on 422 patients

Table 1. Major physiologic and pathologic causes of hyperprolactinemia

<i>Physiologic</i>	<i>Pregnancy</i> <i>Breastfeeding</i> <i>Breast stimulation</i> <i>Sleep</i> <i>Stress</i>
Pathologic	
Pituitary disorders	Prolactinoma Mixed pituitary adenoma Cushing's disease Acromegaly Non-secreting adenomas Pituitary stalk section or tumours Lymphoid hypophysitis
CNS disorders	Tumours Granulomatous disorders Vascular disorders Autoimmune disorders Hypothalamic tumour and metastasis Cranial irradiation Seizures
Systemic diseases	Severe hypothyroidism Chronic renal failure Polycystic ovary syndrome Chest wall trauma Herpes Zoster

on antipsychotic medication has shown that the neuroleptic therapy is strongly associated with hyperprolactinemia with a significantly higher prevalence among patients on typical antipsychotics than atypical antipsychotics (8).

Table 2. Medication causing hyperprolactinemia

Antipsychotics
Phenothiazines
Thioxanthenes
Butyrophenones
Atypical antipsychotics
Antidepressants
Tricyclic antidepressants
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Opiates and Cocaine
Antihypertensive Medication
Verapamil
Methyldopa
Reserpine
Gastrointestinal Medication
Metoclopramide
Domperidone
Histamine 2 receptor blockers
Estrogens

Duration of treatment, age, gender and antipsychotic potency all contribute to the severity of hyperprolactinemia. This side effect is more likely to be seen in adolescents and premenopausal women (8, 9). It has been shown that hyperprolactinemic effect is a dose-related (10). Serotonin is responsible for suckling-induced prolactin release and nocturnal surges. Antipsychotics with serotonergic effects can also stimulate prolactin release via this pathway. However, the prolactin elevation due to serotonin effects are typically milder compared to the dopamine antagonist effects of these drugs. In drug induced hyperprolactinaemia, the prolactin levels are usually <100ug/l. However, some drugs such as risperidone and phenothiazines can give rise to a prolactin level exceeding > 200ug/l (10).

The older generation, typical antipsychotics are frequently associated with elevated prolactin levels

(11). Rapid elevation of prolactin level is seen after intramuscular injections whereas, with oral drugs, it takes about one week for the levels to rise, which becomes constant thereafter. However, the prolactin levels can get normalized within 48 – 96 hours after discontinuation of these drugs. Among typical antipsychotics, Haloperidol is considered to be the most potent drug causing hyperprolactinaemia (7). With haloperidol, rapid elevation of prolactin to a peak level of about 30-50ng/ml occurs within 6 to 9 days and then reach a plateau and remain constant below a level of <70ng/ml (12). However, a dose-dependent increase in prolactin levels has been reported in 40 – 90% of patients treated with most of the other phenothiazines (13).

Risperidone that belongs to a newer class of antipsychotics, atypical antipsychotics, can cause even higher levels of prolactin than typical antipsychotics (12, 14). Its' dose dependent dopaminergic and serotonin antagonistic actions are mainly responsible for the hyperprolactinaemia with this drug. The prevalence of hyperprolactinemia is so common and it is seen in 70 – 100% among patients on risperidone (15). In contrast, olanzapine and quetiapine have lesser effects on prolactin release where the prevalence of hyperprolactinaemia is about 10 to 40%, and with clozapine, it is less than 5% (7). This discrepancy is mainly due to the difference in the occupancy of the D2 receptors of the pituitary, which is an organ situated outside the blood brain barrier. Risperidone has a higher affinity to D2 receptors in the pituitary, causing a significant hyperprolactinemia (16), whereas the atypical antipsychotics have a weaker affinity for the D2 receptors. It is postulated that the transient binding of these drugs to the D2 receptor and also the agonist as well as antagonist effects at the receptor level are mainly responsible for the weaker effects of these drugs on prolactin release.

Antidepressant medication

Anti-depressive drugs exert their effect on prolactin release through serotonin pathway. The effects on prolactin are variable and it is not directly related to the therapeutic effect of antidepressants. Data on the incidence of antidepressant-related hyperprolactinemia is scant. Tricyclic antidepressants cause only a mild

hyperprolactinemia and most studies report no change in prolactin levels (17, 18). However, hyperprolactinaemia due to clomipramine is thought to be common (19). Monoamine oxidase inhibitors have shown to act as weak stimuli for prolactin elevation (18, 20). Fluoxetine, a selective serotonin reuptake inhibitor, appears to cause a modest elevation of prolactin levels (21). However, the hyperprolactinaemia associated with this class of drugs are generally mild and causes asymptomatic (22, 23).

Prokinetics

Metoclopramide and domperidone are notoriously known for its hyperprolactinemic effect. Both act via dopamine antagonistic mechanism. However, metoclopramide has an additional inhibitory effect on serotonin receptors of the chemoreceptor trigger zone of the central nervous system. Therefore, metoclopramide is considered to be one of the potent stimuli for prolactin release and the levels can be high as 15-fold in patients on chronic metoclopramide therapy (24). It can be associated with amenorrhoea, galactorrhoea, gynaecomastia and impotence (25).

Anti-hypertensive Medication

Verapamil causes short and long-term increase in basal prolactin secretion. In an outpatient clinic survey among patients taking verapamil, 8.5% patients reported having a high prolactin level (26). However, the other calcium channel blockers do not seem to have an effect on prolactin secretion (27). Methyldopa causes moderate hyperprolactinemia by inhibiting the enzyme, aromatic-L-amino acid-decarboxylase, which converts L- dopa to dopamine. With a single dose of alpha-methyldopa (750 to 100mg), a rapid rise in prolactin occurs, reaching the peak concentration within 4 to 6 hours. Chronic methyldopa therapy is associated with a three to four-fold rise in the basal prolactin levels. Significantly high serum prolactin levels have also been reported among patients who used to be on centrally acting antihypertensive, reserpine, which is now obsolete in practice.

Opiates

Opiates can cause both short and long-term increase in prolactin levels and the effect is predominantly through μ receptors. However, the hyperprolactinaemia that we see with group of drugs are very mild (28, 29)

Estrogens

The role of estrogens in hyperprolactinemia is controversial. Some studies have shown elevated prolactin in 12 to 30% of women, where as some have shown no or minimal increase while on oral contraceptive pills (30-33). However, the doses of estrogen that are used in hormone replacement therapy has not demonstrated hyperprolactinemia (22).

Management of drug-induced hyperprolactinemia

Patients with hyperprolactinaemia need to be evaluated properly and treated accordingly. In a patient with symptomatic hyperprolactinemia, it is imperative to identify medication as a cause at the outset itself. In addition to drug-induced hyperprolactinaemia, mild prolactin elevation can be seen with prolactin-secreting pituitary microadenomas as well as non-functioning pituitary tumours. Therefore, it is important that proper evaluation is done before reassuring the patient.

A careful history with the timing of onset of symptoms and initiation of drugs is of paramount importance.

When drug-induced hyperprolactinaemia is suspected and once the culprit agent is identified, there are several approaches that we can try to differentiate this from other causes of hyperprolactinaemia (22).

1. Discontinuation of the offending drug: the prolactin levels get normalized in 3-4 days after stopping the offending drug. Measuring the prolactin levels 3-4 days of drug withdrawal is the easiest measure to differentiate from other causes of hyperprolactinaemia. However, this should be done with caution especially in patients with antipsychotic

drugs where the underlying psychosis can get aggravated.

2. Substitution of the offending drug ("switch therapy"): substitution of the offending drug with an alternative drug with a similar action that does not cause hyperprolactinemia is another way or overcoming this problem. Use of atypical antipsychotic agents such as olanzapine, clozapine or quetiapine for traditional antipsychotic medication is a good example. However, this should be attempted with careful consideration after consultation with the attending psychiatrist or the physician (34). If such substitution is not possible, imaging of the pituitary will have to be considered to exclude any mass lesions.

3. When hormone replacement such as estrogen and testosterone for hypogonadism is the reason for hyperprolactinaemia, treatment of the underlying problem and continuation of the offending drug is a challenge. If prevention of osteoporosis is the primary objective of the treatment, alternative medication such as bisphosphonate can be considered in this kind of situations.

4. Dopamine agonists therapy

There is a theoretical risk of exacerbating the psychotic symptoms with the use of dopamine antagonist therapy in patients with antipsychotic medication induced hyperprolactinaemia. However, bromocriptine has been used without major problems (22). There is evidence to suggest that cabergoline can be used safely in patients with antipsychotic medication without exacerbating the psychotic symptoms and without having any alteration in antipsychotic effects of these medications (35). However, it is advisable to use these drugs with extreme caution with the close consultation of a psychiatrist only in patients (36, 37).

5. Aripiprazole

It is a unique atypical antipsychotic agent with partial agonist activity at the D2 receptor. Recent studies have shown aripiprazole as a potential therapeutic option for drug-induced hyperprolactinemia. Limited data have shown that it can be used as an add-on to the ongoing therapy or as switch therapy, by substituting with the original drug (38).

CONCLUSION:

Drug-induced hyperprolactinaemia is a common clinical problem and antipsychotic agents are the commonest culprits. If symptomatic, this problem needs to be properly evaluated and treated accordingly to avoid long-term complications related to associated hypogonadism.

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