Anti Psychotic Induced hyperprolactinaemia

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Abstract

Hyperprolactinaemia has for decades been an inevitable and neglected side-effect of antipsychotic medication. The recent introduction of prolactin-sparing antipsychotic agents makes a re-examination of this problem timely. This article aims to review the literature on antipsychotic induced hyperprolactinaemia and its consequences. A literature search was made for key articles, supplemented by cross referencing. During antipsychotic treatment prolactin concentrations can rise to ten times normal levels or above and existing data indicate that a large number of female patients have amenorrhoea with or without galactorrhoea. Survey data, however, suggest that clinicians underestimate the prevalence of these conditions. Antipsychotic-induced hyperprolactinaemia should become a focus of interest in the drug treatment of psychiatric patients.

Key words : ***Antipsychotics, hyperprolactinemia, prolactin.***

Introduction

Prolactin is a polypeptide hormone that exists as a number of isoforms and is involved in a number of physiological processes. Hyperprolactinemia is elevation of prolactin above the norm and can occur due to various causes including side effect of conventional and some second generation antipsychotics. Hyperprolactinemia has been shown to have many physiological consequences, some of them quite severe including sexual dysfunction, osteoporosis and behavioural effects (hostility, anxiety & depression).[1] Hyperprolactinemia is a disorder of the hypothalamo-pituitary-gonadal axis but may be seen as a side effect of typical and atypical antipsychotics as well.[2] It has a prevalence of 0.4% in the general population and may be as high as 9-17% in the reproductive age group.[3] The present paper reviews the physiology and pathology of hyperprolactinemia and management of antipsychotic induced hyperprolactinemia.

The Neurophysiology of Prolactin

Prolactin is a polypeptide hormone secreted by the lactotorph cells of anterior pituitary gland. Prolactin secretion shows circadian rhythm[4], with highest levels occurring during the night and nadir occurring during the afternoon and evening.[5] Normal basal levels of serum prolactin vary between 5 to 25ng/ml in females and 5 to 15ng/ml in males.[6] Levels vary as per phase of menstrual cycle and can also vary according to age. The regulation of prolactin secretion is controlled by various endogenous agents that are released from or act through the hypothalamus via the hypothalamic pituitary portal vessels in response to various stimuli, including stress, sleep and suckling during breast feeding. Factors such as serotonin, estrogens and thyrotropin releasing hormone stimulate prolactin secretion, whereas gama amino butyric acid and acetylcholine inhibit secretion.

Most importantly, prolactin synthesis and secretion by pituitary lactotorph cells is tonically suppressed by hypothalamic dopamine traversing the portal venous system to impinge on lactotorph D2 receptors.[6] Prolactin itself can cause dopamine release from hypothalamus and thus forms a negative feedback loop. Different isoforms of prolactin have different physiological functions and clinical effects.[7] Apart from its well established function in stimulation and maintenance of lactation, prolactin has been found to be involved in over 300 separate functions including water and electrolyte imbalance, growth and development, reproduction, endocrinology and metabolism and immunoregulation.[5] In terms of affecting brain and behaviour, prolactin is shown to increase brain neurogenesis in pregnant mice. Prolactin stimulates an increase in the number of neural progenitors in the forebrain which then migrate to the olfactory bulb. Here these additional neurons are thought to play a role in maternal behaviour because olfactory behaviour is critical for recognition and rearing of offspring.[8] In humans, prolactin also plays a role in the regulation of sexual activity and behaviour. It has been observed that orgasms

cause large and sustained (60 min) increase in plasma prolactin in both men and women9, which is associated with decreased sexual arousal and function. Furthermore, increased prolactin is thought to promote behaviours that encourage long-term partnership.[10]

General aspects of Hyperprolactinaemia

Hyperprolactinaemia is diagnosed when serum prolactin concentrations are greater than 20-25ng/ml (400-500mU/l) on two separate occasions.[11] The Endocrine Society Clinical Practice guidelines (2011) state that in

order to establish the diagnosis of Hyperprolactinaemia, a single measurement of serum prolactin; at a level above the upper limit of normal confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress.[12] Dynamic tests of prolactin secretion using TRH, Ldopa, nomifensine, and domperidone are not superior to measuring a single serum prolactin sample for the diagnosis of Hyperprolactinaemia.[13] A single determination is sufficient to establish the diagnosis, but when in doubt, sampling can be replaced on a different day at 15 to 20 min intervals to account for possible prolactin pulsatility.[14]

Hyperprolactinaemia most commonly results from a disorder of hypothalamic –pituitary axis[15] and its causes can be grouped as physiological (sleep, sexual intercourse, pregnancy, nursing) and pathological (pituitary tumours most commonly prolactinomas, hypothyroidism and pharmacological).[16] Traumatic childhood experiences such as parental separation or living with alcoholic father have been reported to produce increased predisposition to hyperprolactinemia.[8] Medications that elevate prolactin levels include antipsychotics, oral contraceptive pills, oestrogens, tricyclic antidepressants, serotonergic drugs, propranolol, methyldopa and reserpine.[8]

Antipsychotics and hyperprolactinemia

Hyperprolactinema is thought to be caused by antipsychotic agents blocking the D2 receptors on the lactrotroph cells and their effects on the tubero-infundibular dopamine pathway, thus preventing inhibition of prolactin secretion. Furthermore it has been suggested that the degree of elevation of prolactin co relates with the degree of occupancy of D2 receptors in excess of 50%.[17]

Traditional first generation antipsychotic drugs

Most studies have shown that conventional anti psychotics are associated with a 2 to 10 fold increase in prolactin levels.[17] The increase in prolactin that occurs due to use of conventional anti psychotics develops over the 1st week of treatment and remains elevated throughout the period of use. Once the treatment stops, the prolactin levels return to normal within 2-3 weeks.[18] It has been suggested that tolerance can develop in patients treated chronically with anti-psychotics and that prolactin levels gradually decline with extended antipsychotic use.19 Prospective studies with an open or double-blind design have shown that medium-term treatment (3–9 weeks) with therapeutic dosages increases mean baseline prolactin levels up to ten-fold.[20-22] Low daily dosing regimens (e.g. 200mg chlorpromazine) can cause significant prolactin elevations and levels have been reported to increase in a dose-dependent manner up to about 600mg chlorpromazine equivalents.[23]

Second Generation Antipsychotic Drugs

In general second generation anti psychotics produce lower increase in prolactin than conventional agents.[24] Risperidone produces the most elevation in prolactin levels amongst the second generation agents.[24] Olanzapine, Zotepine, Amisulpiride and Quetiapine are also associated with increase in prolactin levels. An analysis of double blind studies of risperidone in schizophrenic patients showed that there is dose dependent increase in prolactin concentrations in both men and women.[25] In a randomised, double-blind, parallel group study that compared treatment with amisulpride (1000mg daily) and oral flupentixol (25mg daily) in 32 men and women with schizophrenia who were free of oral antipsychotic medication for at least 4 weeks and depot neuroleptics for at least 3 months. After 4

weeks of treatment mean baseline prolactin levels were significantly elevated in both groups, in the amisulpride group by a factor of 10 and in the flupentixol group by a factor of 5. The difference between amisulpride and flupentixol treatment was significant in the women patients.[26]

Pooled data from two large, randomised, double-blind, controlled clinical trials comparing 8 weeks of treatment with fixed daily doses of risperidone (1mg, 2mg, 4mg, 6mg, 8mg, 10mg, 12mg and 16mg), haloperidol (10mg and 20mg) and placebo. Prolactin measurements were taken at end-point in 259 women. Levels in the risperidone group were increased above the normal range in proportion to the dose and their mean was significantly higher than in women treated with 10mg (but not 20mg) of haloperidol.27 Whether risperidone has a greater effect on prolactin secretion than equivalent doses of haloperidol, as reported in a small 54-week continuation study, requires further analysis.[28]

In another study, researchers measured prolactin levels in 29 men and women with chronic schizophrenia after a 2-week standardising therapy with oral fluphenazine (20mg daily) and 6 weeks after switching to clozapine (mean dose 400mg daily) or risperidone (mean dose 6mg daily). At the end of fluphenazine treatment prolactin levels were increased by about twice the normal reference range in each group. After switching, levels decreased highly significantly into the normal reference range in the clozapine group, whereas they did not change significantly in the risperidone group.[29] Preliminary evidence indicates that zotepine can also cause prolactin elevation in humans after both acute and chronic treatment.30 Studies of patients who are treatment naive or who have been withdrawn from treatment for a period of time indicate that schizophrenia per se does not affect prolactin concentrations. In such patients, prolactin concentrations are not

different from controls31 although the circadian cycle in schizophrenic patients appears to be advanced by 1 to 1.5 hours, an advance that also occurs in patients on antipsychotics.

Clinical manifestations of hyperprolactinemia

Hyperprolactinemia may remain clinically asymptomatic. Women who suffered from hyperprolactinaemia consisting mainly of the trimeric form of prolactin (microprolactin) neither showed any clinical symptoms nor suffered from reproductive dysregulation, despite elevated prolactin concentrations (700-1600mg/l).32 It is thought that these polymeric forms of prolactin assays can be detected by current prolactin assays33, but they are not necessarily physiologically active. Clinical presentation may include hypogonadism, decreased libido and osteopenia in both sexes; infrequent or absent menstrual cycle, galactorrhoea and infertility in women. Low sperm count and reduced muscle mass in men.34 However, in addition to the effects of hyperprolactinaemia on sexual function and reproductive health, hyperprolactinaemia has been linked to other disorders as well.

While untreated schizophrenia patients exhibit decreased sexual desire35, antipsychotic treatment is associated with restoration of sexual desire, yet it entails erectile, orgasmic and sexual satisfaction problems.36 In women receiving antipsychotics, the incidence of menstrual disturbances is 15 to 50 % There may be infrequent or absent menstrual cycles.37 The feedback loop that links prolactin and dopamine also affects the release of gonadotropin releasing hormone (GnRH), which like prolactin , is inhibited by dopamine. When the inhibitory effect of dopamine on prolactin is lost (as in treatment with dopamine antagonist), hyperprolactinemia occurs. This rise in prolactin levels causes a concomitant rise in

dopamine levels which in turn inhibits the release of GnRH .The lower levels of GnRH lead to the symptoms of hypogonadism that are a primary consequence of hyperprolactinemia.[38] The association between hyperprolactinemia and osteoporosis appears to be mediated by oestrogen deficiency secondary to sustained prolactin elevation, although prolactin itself may have a direct effect on bone formation.[39] Some studies state that bone loss occurs secondary to hyperprolactinemia mediated sex steroid attenuation. Spinal bone density is decreased by approximately 25% in women with hyperprolactinemia[40] and is not necessarily restored with normalization of prolactin levels. Several studies have linked hyperprolactinemia to an increase in risk of breast cancer in women. The possible mechanisms include increase in synthesis and expression of prolactin receptors in malignant breast tissue and a prolactin-induced increase in DNA synthesis in breast cancer cells in vivo.[41]

Managing antipsychotic induced hyperprolactinemia

When treating antipsychotic induced hyperprolactinemia, decisions should be made on an individual basis after a full and frank discussion with the patient. These discussions should include consideration of benefits of antipsychotic therapy as well as potential impact of any adverse effects. The importance of discussing symptom impact is highlighted by data showing that only a minority of patients discontinue their antipsychotic medication because of breast tenderness, galactorrhoea or menstrual irregularities.42

The Endocrine society Clinical practice guidelines, 2011 state that no treatment is necessary in an asymptomatic patient with drug induced hyperprolactinemia.43 Increase in prolactin could be due to formation of macroprolactin which does not have serious consequences for the patient. If there

are doubts about the cause of hyperprolactinemia, other possible causes especially tumours must be excluded.44 Sexual side effects are the commonest cause for non compliance. The decision to change the current antipsychotic to an agent with lower dopamine antagonist property or aripiprazole (an atypical antipsychotic with both Dopamine agonist and antagonist activity that can lower prolactin and reverse hyperprolactinemia side effects) should be made on the basis of risk benefit estimation.45

Adjunctive therapies have also been tested to reduce the symptoms of hyperprolactinemia, but these are associated with their own risks. Oestrogen replacement can prevent the effects of oestrogen deficiency, hypogonadal symptoms, but it carries the risk of thromboembolism.[46] Dopamine agonists such as Cabergoline and Bromocriptine have been suggested for the management of hyperprolactinemia in patients receiving antipsychotics, but these are associated with side effects and may worsen psychosis.47

Conclusions

Endocrine symptoms occur in a large proportion of women treated with prolactin elevating antipsychotic drugs. These symptoms can cause significant distress and may affect compliance with medication. A significant proportion of premenopausal women with psychotic disorders may be at risk of premature bone loss and other consequences of chronic hypooestrogenism due to long-term antipsychotic medication. The presence of menstrual irregularities, breast symptoms and sexual dysfunction should be assessed before and during treatment with prolactin-elevating drugs and management options should be discussed with the patient. Thus management of antipsychotic hyperprolactinemia should exclude all

other causes, involve a regular monitoring of adverse effects and include a regular risk benefit discussion with the patient.

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