Mirtazapine-Induced Galactorrhea: A Case Report

To the Editor: Mirtazapine is a well-established tetracyclic antidepressant with a unique mechanism of psychopharmacological action: Serotonin release is increased through noradrenergic stimulation of excitatory alpha$_1$-adrenergic receptors located on serotonergic cell bodies and by blockade of the inhibitory alpha$_2$-adrenergic presynaptic heteroreceptor located on serotonergic neurons.[1] Mirtazapine also blocks serotonin receptors (5-HT$_{2A}$, 5-HT$_{2C}$, and 5-HT$_3$) and augments adrenergic neurotransmission.

The German drug safety program in psychiatry (AMSP) reports severe adverse drug reactions (ADR) from mirtazapine; most common were increased liver enzymes, collapse, and cutaneous edema. Rare ADR were subclinical pancreatitis, restless-legs syndrome, and weight gain (BMI >30).[2] Mirtazapine seems to be relatively nontoxic, since case reports with ingestions of 30 to 50 times the maximum allowed daily dose describe drowsiness and somnolence as the main ADR, and patients achieved full recovery.[3]

Symptoms of hyperprolactinemia, such as galactorrhea, amenorrhea, and sexual dysfunction, are well-known ADR of antipsychotic medication. Prolactin is secreted by the pituitary gland, with high secretory activity and pulsatility. Dopamine is considered the primary physiological factor inhibiting tonically prolactin secretion. Dopaminergic cells of the hypothalamus have projections to the median eminence to release dopamine into the portal vessels, by which it reaches the lactotrophs in the anterior pituitary. This system is known as the 'tuberoinfundibular dopamine pathway' (TIDA). A second inhibitory pathway involves dopamine release into the blood supply of the posterior pituitary. Through that pathway, dopamine reaches the lactotrophs via short portal vessels. Release of prolactin as a side effect of antipsychotics is mediated through the TIDA by direct blockade of D_2 receptors located on the lactotrophs.[4]

Hyperprolactinemia-related ADR rarely occur under antidepressant therapy,[2,5] and are mediated by serotonin. The responsible mechanism seems to be indirect and modulating, and is not fully understood.[4] Concerning mirtazapine, prospective pilot studies have shown no elevation of prolactin levels,[5] and no case reports on hyperprolactinemia under mirtazapine treatment have been published in English-language journals. However, case reports of two geriatric male patients are available in French and Spanish language (when conducting a PubMed search for "galactorrhea AND mirtazapine"). One reports on an 89-year-old man who developed gynecomastia and galactorrhea without hyperprolactinemia after 21 months of mirtazapine treatment,[6] and one reports gynecomastia in an 85-year-old man after 7 weeks of medication with mirtazapine.[7]

We present a case of a 28-year-old inpatient woman, with major depression, comorbid borderline personality disorder, and PTSD, diagnosed according to DSM-IV, who developed galactorrhea with delayed elevation of prolactin under mirtazapine treatment. Four weeks after adjusting the dosage to 30 mg/day, spontaneous galactorrhea, with soaked clothing and mastodynia appeared, which are signs for severe ADR according to AMSP.[2] Morning serum prolactin levels were not elevated in initial measurement, 12 days later, an elevation was seen (32.1 μg/l; normal range: 4.79–23.3 μg/l). Other clinical symptoms were fatigue and extended subcutaneous edema of the trunk and extremities. To exclude other etiology, several examinations were performed. A cerebral magnetic resonance tomography did not show pituitary alterations. Referral for gynecological consultation yielded typical findings of galactorrhea; cytological, sonographic, and mammographic examinations showed no signs of malignancy. After discontinuation of mirtazapine and change to escitalopram, serum prolactin normalized, and edema and galactorrhea remitted within 1 week. The psychopathological stabilization already attained by mirtazapine persisted. A transient elevation of liver enzymes (ASAT, max.: 118 U/l; normal range: 10–35 U/l; ALAT, max.: 56 U/l, normal range: 10–35 U/l), and creatine kinase (CK, max.: 9,100 U/l; normal range: below 139 U/l) that was observed during the switching period resolved within a few days, and was interpreted as most likely unrelated to pharmacotherapy and caused by excessive fitness training after mood improvement.

In conclusion, we found mirtazapine-induced galactorrhea with delayed elevation of serum prolactin accompanied by other ADR-like edema. A prolactin increase induced by mirtazapine is pharmacologically plausible. Serotonin indirectly elevates prolactin release through different, not yet comprehensively understood mechanisms.[4] Two main mechanisms are

discussed: 1) the paraventricular nucleus located in the hypothalamus, a regulatory organ of the neuroendocrine system, contains postsynaptic serotonergic 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors. Serotonin receptor agonists binding on these receptors in the paraventricular nucleus may elevate prolactin through two possible pathways involving either release of oxytocin or vasoactive intestinal peptide, both considered as putative prolactin releasing factors; 2) an alternate pathway for serotonin-induced prolactin release is mediated by inhibition of the tuberoinfundibular dopamine cells. Inhibition either may happen through direct inhibition of dopamine cells or, since there seems to be little direct synaptic contact between serotonergic fibers and dopamine cells,[8] through volume transmission of serotonin in the region or via serotonergic stimulation of assumingly interneuronal GABAergic neurons in the vicinity of the TIDA dopamine cells. As these GABAergic cells carry 5-HT_{1A} receptors, their stimulation by serotonin would result in an inhibition of TIDA cells, resolving the tonic inhibition of prolactin release.[4]

As 5-HT_{2A} and 5-HT_{2C} receptor stimulation may also be responsible for prolactin increase, mirtazapine is the only antidepressant that blocks these serotonin receptors; this might explain the lower rate of hyperprolactinemia compared with other antidepressants. Nevertheless, this ADR is still possible as seen in our patient.

Hyperprolactinemia has acute and chronic effects, and women tend to be affected more. Acute symptoms comprise oligo- or amenorrhea, loss of libido, breast tenderness, and galactorrhea in women. Men can suffer from gynecomastia, impaired libido, and erectile dysfunction. Chronic hyperprolactinemia is also associated with reduced bone mineral density and increased risk of osteoporotic fracture, arguably with breast cancer and possibly prostate cancer.[9] Also, subtle alterations in prolactin levels might elucidate unexplained infertility in women.[10] Since hyperprolactinemia is difficult to diagnose in men and especially in postmenopausal women, who often receive mirtazapine as a treatment for major depressive disorder or, for example, as part of a complex pain treatment, suspected prolactin elevation due to mirtazapine need clinical attention. Research in this field that is currently mainly focused on SSRIs[4] should be extended to mirtazapine.

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