

HYPERPROLACTINAEMIA WITH AMISULPRIDE

Klementina Ružić¹, Tanja Grahovac¹, Mirjana Graovac¹, Elizabeta Dadić-Hero²,
Dubravka Šepić-Grahovac³ & Vladimir Sabljic¹

¹University Psychiatric Clinic Rijeka, Clinical Hospital Centre Rijeka, Croatia

²Community Primary Health Centre, Primorsko-goranska county, Croatia, Department of Social Medicine and Epidemiology, School of Medicine, Rijeka, Croatia

³Policlinic for Neurology and Psychiatry "Interneuron", Rijeka, Croatia

SUMMARY

Psychopharmaca are used in treatment of psychiatric illnesses and disorders, among other therapeutic possibilities. The choice of the psychopharmaca is determined by the specific psychopathology of the patient, within the diagnostic categories, according to the current classification of diseases and disorders. With the advances in pharmaco industry, the range of drugs used in the everyday clinical practice is occurring at a very rapid pace.

Antipsychotic medications are used in treatment of mainly psychotic disorders. However, the new generation of antipsychotics, due to their specific receptor affinities, is sometimes used in treatment of affective disorders as well.

We are reporting a case of a female patient who was hospitalized several times. Amisulpride was introduced in the treatment and due to a series of unfortunate events and changes that followed (i. e. frequent hospitalizations and changes of therapists, different mental institutions) dose of amisulpride was gradually increased to its antipsychotic doses, which did not help achieve therapeutic benefits, but serious side effects.

Key words: mixed anxiety- depressive disorder- amisulpride- hyperprolactinaemia

* * * * *

INTRODUCTION

The object of psychiatric treatment is human life and mental health and every psychiatrist's action is directed towards that target. Respecting this principle, a psychiatrist has a freedom of choice which psychopharmaca and other therapeutic procedures to choose as a part of a treatment. Psychiatrists are autonomous in their choice, as well as in their therapeutic dosage of psychopharmaca, which they choose according to the best of their knowledge and experience. During the therapeutic process, it is the psychiatrist who has a more active role. The patient is instructed to trust his/her knowledge, abilities and good intentions. The choice of an efficient psychopharmaca lies in the prevailing group of symptoms within the diagnostic category of the psychiatric illness or disorder.

A large number of medications used in the psychiatric practice can cause various side effects which must be communicated to the patient and identified as soon as possible. A common and the most important features of antipsychotics is that they are dopaminergic receptor antagonists (Uzun et al. 2005). Antipsychotics can also cause endocrine side effects, among which we will focus on the subject of our clinical case report - hyperprolactinaemia.

Hyperprolactinaemia is more common in treatment of first-generation antipsychotics. As second- and third-generation antipsychotics have a weaker affinity for D₂ dopamine receptors, hyperprolactinaemia is less common when such medication is used (i. e. except for sulpiride) (Uzun et al. 2005).

Amisulpride, a substituted benzamide derivative, is a second-generation antipsychotic that preferentially binds to D₂/D₃ receptors in limbic rather than striatal structures (Raj & Sidhu 2008).

As with any other medication, amisulpride can have various side effects which may cause hyperprolactinaemia. Although amisulpride is considered to be a prolactin-raising atypical antipsychotic drug, a limited number of studies have documented the extent of its prolactin-elevating properties (Paparrigopoulos et al. 2007).

Hyperprolactinaemia may occur in patients receiving amisulpride at low dose of 50 mg/day and results in galactorrhoea, amenorrhoea and sexual dysfunction (Raj & Sidhu 2008).

Amisulpride in antipsychotic doses can induce hyperprolactinemia. Even low doses of amisulpride used as an augmentation to antidepressant treatment, benzodiazepines or in monotherapy seem to be associated with hyperprolactinemia. The co-medication of antidepressants and benzodiazepines can potentially increase intensity of prolactinemia (Kopecek et al. 2004).

The risk of side effects caused by antipsychotics is individual and it does not depend solely on the therapeutic dose. High doses of antipsychotics can increase the risk of some side effects and speed them up, some of which can be detrimental to the patient's health or even prove to be fatal.

In the clinical case report that follows we will describe a patient in whose treatment of anxiety-depressive disorder amisulpride was introduced. She has developed hyperprolactinaemia to antipsychotic doses of amisulpride.

CASE REPORT

Female patient, aged 51, unemployed, married, mother of two adult children was hospitalized five times within a year due to mental disorders of mixed anxiety-depressive features. A year of the treatment later the remission of psychiatric symptoms was not achieved.

The first hospitalization followed due to mental disorders that lasted for about a year prior to the hospitalization. Symptoms that the patient described were headaches, dizziness, occasional and sudden palpitations, chest pressure, feeling of choking, tingling sensations in her left hand and leg. She was afraid of the symptoms recurring and because of that isolated herself from the others; she was feeling annoyed by everything, apathetic and dejected. She lost her appetite (lost 20 kg) and had severe sleeping disorders.

Routine tests (i. e. lab analyses, EEG, ophthalmologic test) showed normal results, and psychodiagnostics established borderline personality.

Due to prominent psychopathology, the patient was treated with a combination of citalopram (20 mg/day), alprazolam (1.5 mg/day), fluphenazine (3 mg/day), zolpidem (5 mg/day).

She was diagnosed with the mixed anxiety-depressive disorder (F 41.2), psychosomatic illness (F 54) and borderline personality (F 60.3), according to the valid diagnostic criteria ICD-10 and DSM IV.

Three months later, the patient was hospitalized again due to worsened mental condition, now predominantly depressive in its manner (i.e. apathy, loss of interest, concentration difficulties, inner restlessness/tension) along with the existing symptoms she focused on (i.e. head pressure, dizziness, palpitations, tingling sensations in arms and legs). Routine tests did not show any discrepancies.

Psychopharmaca were adjusted: citalopram (30 mg/day), quetiapine (600 mg/day), lamotrigine (200 mg/day), alprazolam (1 mg/day). When the patient was discharged from the hospital, the diagnoses remained unaltered (F 41.2, F 54, F 60.3).

A week after the patient was discharged from the hospital, she was admitted again with her mental condition unchanged, with somatic fixation, due to which a broad spectrum of diagnostic procedures was done (i. e. otolaryngologists, internist, neurologist, dermatologist, CT and UTS of abdomen) that showed no significant changes at the physical level.

Amisulpride was introduced for the first time during this stay and was titrated to a stable dose of 300 mg/day, combined with citalopram (10 mg/day), lamotrigine (200 mg/day) and alprazolam (1 mg/day).

A month later, another hospitalisation ensued due to the same symptomatology, but now in a different mental institution. Correction of psychopharmaca was made. Daily dosage of amisulpride was gradually increased to 600 mg/day combined with daily dosage of paroxetine 40 mg, alprazolam 1 mg, lamotrigine 200 mg and zolpidem 10 mg.

Last hospitalization ensued three months later. On mental level the same symptomatology persists (i.e. anxiety and depression). New symptom is galactorrhea which the patient noticed during the last month. Upon admittance to the hospital, lab tests of prolactin in serum were done (2881 mIU/L) and amisulpride therapy was gradually discontinued. Control analyses of prolactin in the serum were done 10 and 28 days after the first measuring, respectively. Values of prolactin in the serum showed a decreasing trend (2136 mIU/L and 159.3 mIU/L, respectively).

Diagnostics was repeated during this stay in the hospital. Analysis and evaluation of all symptoms detected no elements of another mental disorder, other than anxiety and depression with borderline personality.

The patient was then prescribed duloxetine 60 mg/day, diazepam 20 mg/day, lamotrigine 200 mg/day, and olanzapine 5 mg in the evening dose.

For the last 6 months the patient has been regular in the ambulatory treatment, thus creating preconditions for continuing such a treatment (i.e. during the last year of treatment it was not possible to proceed with the ambulatory treatment, which is the objective of every hospitalisation). Symptomatology is now much milder in its intensity, but still inadequately remitted. Level of prolactin is in referent values.

DISCUSSION

In everyday clinical practice we come across difficulties that can affect the outcome of treatment. The objective of this analysis is to point out at hyperprolactinaemia as a side effect of amisulpride. A number of issues and dilemmas have been raised retrospectively, ranging from medical and conceptual to ethical and moral. Furthermore, the need to stress the importance of individual/personalized approach in treatment of psychiatric patients has re-emerged.

Hyperprolactinaemia that has developed as a side effect of amisulpride in this case was a result high dose of the medication. Analysis of the occurrence of this side effect has brought us back at the beginning of the treatment and to a new diagnostic evaluation of the symptoms.

By re-evaluating the symptomatology on the one hand and the analysis of the psychopharmacologic treatment on the other, no elements of another psychiatric illness or disorder were found, other than the previously diagnosed mixed anxiety-depressive disorder and borderline personality.

Given the psychopathology that has remained within the framework of mixed anxiety-depressive disorder (F 41.2) from the beginning of the treatment, the indication for administration of antipsychotics was called into question. Analysis of the data obtained from the patient, as well as the evaluation of the leading symptoms, gave us no elements that could justify introduction of high (antipsychotic) doses of any antipsychotics, not even amisulpride. There was no justified administration for higher doses of amisulpride, due to the fact that the

patient never manifested psychotic symptoms. Symptomatology was always, and has remained, at the level of mixed anxiety-depressive disorder.

Even though psychopathology originating from the borderline personality can be indicative of the treatment of antipsychotics, given the lack of psychotic symptoms of this patient we believe that lower doses of antipsychotics would have been sufficient.

In the presented case administration of higher doses of antipsychotics, not even amisulpride, did not give the results expected, given the existing symptoms, other than one serious side effect (i.e. hyperprolactinaemia). Doses of amisulpride per se were increased, without previously conducting the re-evaluation of psychiatric symptoms. Diagnosis of disorders, as well as the choice and dose of antipsychotics, was not consistent.

Thanks to current research we know that amisulpride is a prolactin-raising atypical antipsychotic drug which can cause hyperprolactinaemia at even low therapeutic doses (Raj & Sidhu 2008). Knowing this, the risk for causing hyperprolactinaemia is higher when higher doses are administered. Therefore, it is medically justified and preferable in practice to monitor prolactin when amisulpride is introduced, as well as during titration of doses.

Administering unrealistically high doses of antipsychotics has proven medically unjustified in this case.

Such treatment goes deep into the basic ethical principles and responsibility of the psychiatrist which have been regulated for centuries - from the Code of Hammurabi, Hippocratic Oath, and the Declaration of Geneva.

Given the obligations and responsibility of the psychiatrist that are regulated by the ethical principles and binding laws on the one hand and rights of psychiatric patients on the other, the question of medical error is eventually brought up. Even though we are reluctant to accept it, it has become a burning issue.

In psychopharmacological treatment the medical error can mean prescribing too high or too low a dose of medication, as well as abrupt discontinuation of medication which can cause severe abstinence disturbances or other psychophysiological disturbances to the patient (Goreta 2010).

Patients with comorbid diagnosis of personality disorders fall into the category of 'difficult and demanding patients' among which the ability of prescribing medication is often put to a test. However, titrating medicines to high doses done in a hurry, without medical validation, should not be our everyday clinical practice. How much do the 'proscribed' limits of hospital treatment contribute to this, aiming solely to reduce cost in health care? The negative outcome of the

treatment could have been affected by the fact that several psychiatric teams treated the patient. This also raises the issue of professional communication. It seems that the development of side effects in our patient and the engagement of the psychiatrist to recover the patient formed a good therapeutic alliance which, thanks to adequate prescription of antipsychotics, resulted in improved psychopathology. Taking everything into consideration there is one thing, however, that remains questionable: Is it possible that a medical error, that is - malpractice, occurred?

CONCLUSION

Antipsychotics of the new generation (i.e. atypical) are relatively safe in situations when their usage is strictly indicated (i.e. according to the symptomatology) and individualized (i.e. according to the patient and their characteristics). The precondition is to recognize the dominant symptoms of the illness within the established diagnosis and then to choose efficient psychopharmaca. Justified administration of antipsychotics and the efficient therapeutic dose have to be carefully evaluated at all times. As with any other medication, atypical antipsychotics can also cause side effects that cannot be safely predicted. Side effects have to be identified as soon as possible and it is necessary to intervene promptly.

Knowledge in psychopharmacotherapy and clinical experience of the psychiatrist can surely help preventing the side effects of antipsychotics. It is necessary to stress the importance of the adequate choice of psychopharmaca. Choosing well has a positive effect on the symptoms of an illness, which is, along with the prevention of side effects, a precondition for developing a therapeutic relationship and a successful psychiatric treatment.

REFERENCES

1. Goreta M. *Profesionalna odgovornost psihijatra. 1st ed. Zagreb: Organizator; 2010.*
2. Kopecek M, Bares M, Svarc J, Dockery C & Horáček J. *Hyperprolactinemia after low dose of amisulpride. Neuro Endocrinol Lett 2004; 25:419-422.*
3. Paparrigopoulos T, Liappas J, Tzavellas E, Mourikis I & Soldatos C. *Amisulpride-induced hyperprolactinaemia is reversible following discontinuation. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31:92-96*
4. Raj R & Sidhu BS. *Hyperprolactinaemia with amisulpride. Indian J Psychiatry 2008; 50:54-56.*
5. Uzun S, Kozumplik O, Mimica N & Folnegović-Šmalc V. *Opis nuspojave psihofarmaka prema pojedinim skupinama lijekova. In: Uzun S, Kozumplik O, Mimica N & Folnegović-Šmalc V, editors. Nuspojave psihofarmaka. 1st ed. Zagreb: Medicinska naklada, Psihijatrijska bolnica Vrapče; 2005; p. 19-28.*

Correspondence:

Klementina Ružić, MD, PhD
University Psychiatric Clinic Rijeka
Clinical Hospital Centre Rijeka, Rijeka, Croatia
E-mail: ruzic.klementina@gmail.com