

TREATMENT OF METHADONE PATIENTS WITH NEUROLEPTIC THERAPY AND HYPERPROLACTINEMIA

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Abstract: According to certain findings, heroin addiction represents a significant medical as well as social problem. It is known that with opioid substitution treatment this disease can be overcome or alleviated. However, the application of this treatment does not always give the expected results, so it is necessary to apply additional neuroleptic therapy until the patients are fully stabilized. But the joint application of substitution and neuroleptic therapy can lead to a series of side effects, one of which is the appearance of hyperprolactinemia.

The aim of this study is to observe the prevalence of symptoms of hyperprolactinemia in patients with poor response to methadone treatment, treated with neuroleptic therapy.

Material and methods: The cross-sectional study evaluated 20 male patients with a mean age of ± 24.13 years treated at the Skopje Psychiatric Hospital with high doses of Sol methadone 80-120 mg/day. All patients had a bad agreement on the methadone treatment, so additional therapy was included, tab. Risperidone with an average dose of 2 mg/day. Participants signed an informed consent to participate.

Patients were assessed using a semi-structured questionnaire specifically designed for the study. Data consisted of age, sex, and symptoms of hyperprolactinemia: amenorrhea, loss of libido, erectile dysfunction, and gynecomastia. The results of this study were analyzed using descriptive methods, t-test and Pearson's correlation coefficient. The p value of statistical significance was set at $p < 0.05$.

Results: The results obtained in our study showed that a certain percentage of methadone patients who were on Risperidone therapy had symptoms of hyperprolactinemia, but the results were without statistical significance $p > 0.05$.

Conclusion: although in our study we obtained a small percentage of patients with symptoms of hyperprolactinemia, care must be taken in patients on methadone treatment who are also treated with neuroleptic therapy due to their synergistic effect, we should always keep in mind the possibility of developing hyperprolactinemia.

Keywords: methadone treatment patients, risperidone, hyperprolactinemia.

1. INTRODUCTION

According to certain findings, heroin addiction represents a significant medical as well as social problem. It is known that with opioid substitution treatment this disease can be overcome or alleviated (Ammari R et al ,2020). However, the application of this treatment does not always give the expected results, so it is necessary to apply additional neuroleptic therapy until the patients are fully stabilized. But the joint application of substitution and neuroleptic therapy can lead to a series of side effects, one of which is the appearance of hyperprolactinemia (Chokhawala K.et al,2023; Koch MT et al,2023)

Mechanism of occurrence of hyperprolactinemia syndrome : The tuberoinfundibulum (TIDA) is comprised of a small number of neurons whose cell bodies are located in the paraventricular nucleus and nuclei arcuate in the hypothalamus while axons project along the central part of the hypothalamus. Dopamine is released from the axons in the pituitary portal capillary system and inhibits the release of prolactin through the action of D2 receptors on the lactophilic cells (laktifilus) located in the anterior part of the pituitary gland (adenohipofiza) (Asa SL et al,2022)

It is considered that the secretion of sex hormones is regulated by the hypothalamic-pituitary axis, that is, through the gonatropic hormone GnRH, which is secreted by the hypothalamus, it acts on the secretion of the pituitary follicle-stimulating hormone FSH, which stimulates the production of sex hormones (Alchabi MS et al,2023).

Hyperprolactinemia has an inhibitory effect on the function of gonadotropin-releasing hormone

So the syndrome of hyperprolactinemia can lead to reproductive dysfunction (anovulation, loss of menstrual cycle, sterility, reduced estrogen and testosterone production) As well as sexual dysfunction, decreased libido, erectile dysfunction, ejaculation problems, impotence (Amato D et al,2019)

The action of antipsychotics is based on blocking the receptors of the neurotransmitter dopamine in the nervous system. Dopamine receptors D2, D3 and D4 are associated with mental illnesses whose action can be blocked by

antipsychotics, they act as strong antagonists. However, blocking D2 receptors can cause side effects that occur to a lesser extent with newer antipsychotic drugs.

What is very important to note is that in all parts of the central nervous system, through D 2 receptors, neuroleptics inhibit i.e. block the production of dopamine, thus also in the area of the hypothalamus they lead to an inhibitory effect on the secretion of dopamine while leading to a state of elevated levels of prolactin, that is, creating HYPERPROLACTINEMIA SYNDROME (Ammari R et al ,2020; Asa SL et al,2022)

According to certain studies, antipsychotics block the inhibition of dopamine on the pituitary gland and cause an increase in prolactin with symptoms of hyperprolactinemia (Amato D et all,.2019)

Different antipsychotic drugs have different effects on serum prolactin levels because some typical antipsychotic drugs have high affinity for dopamine (D2) receptors such as Haldol while a group of atypical antipsychotics have low affinity for D2 receptors such as Olanzapine (Koch MT et all,2023)

The aim of this study is to observe the prevalence of symptoms of hyperprolactinemia in patients with poor response to methadone treatment, treated with neuroleptic therapy.

2. MATERIAL AND METHODS

The cross-sectional study evaluated 20 male patients with a mean age of ± 24.13 years treated at the Day Hospital of heroin addicts department of e Psychiatric Hospital Skopje with high doses of Sol methadone 80-120 mg/day. All patients had a bad agreement on the methadone treatment, so additional therapy was included, tab. Risperidone with an average dose of 2 mg/day. Participants signed an informed consent to participate Exclusion criteria from the study were the transient existence of some acute or chronic somatic diseases (hyperthyroidism, hypertension) as well as pregnancy conditions.

Patients were assessed using a semi-structured questionnaire specifically designed for the study. In the questionnaire, in addition to sociodemographic data (age, gender, marital status, work status, education), the symptoms of hyperprolactinemia were noted: problems with the menstrual cycle and the presence of gynecomastia.

Scale for assessment of sexual functionality in men.: International Index of Sexual Function (IIEF) Questionnaire of 15 questions relating to 4 areas of sexual desire, experience of orgasm, satisfaction from the sexual act and satisfaction from the overall sexual activity

The strength of the symptoms was adjusted in 4 levels: a state without sexual dysfunction, a state with weak sexual dysfunction, a state with weak to moderately pronounced sexual dysfunction, a state with pronounced sexual dysfunction

The results of this study were analyzed using descriptive methods and Pearson's correlation coefficient. The p value of statistical significance was set at $p < 0.05$

3. RESULTS

In our study, comparing the sociodemographic parameters of the examination group before treatment and after treatment with Risperidone, we did not get a result with statistical significance Table. 1

Table 1. Sociodemographic characteristics of the examination group

parameters	Before treatment	After treatment	T test	P level
Married status Y/N %	45%/55%	48%/52%	1,12	0,08
Employment Y/N%	20%/80%	25%/75%	2,14	0,07
Years of education	9 \pm 3,5	10 \pm 2,5	1,64	0,12

Source: The authors

The obtained results in our study indicated that, the symptoms of hyperpolactinemia were represented in a higher percentage in the studied group after treatment with Risperidone but without statistical significance. (Table. 2,3)

Table2. Sexual dysfunctions in the examination group

Group before/after treatment with risperidone	mean	SD	t-test	P level
Libido problems	10,91/12,15	1,25/1,39	0,25	0,08
Problems with experiencing	9,14/11,25	1,12/1,28	0,78	0,06

orgasm				
Dissatisfaction of the sexual act	8,15/11,23	2,1/1,8	0,68	0,05
Dissatisfaction of the overall sexual life	9,93/12,11	1,33/1,36	0,25	0,08

Source: The authors

Table 3. List of others symptoms of hyperprolactinemia

paramtrs	Before/after treatment (%)	T test	P level
Sexual dysfunction	19/25	1,96	0,06
Problems with menstrual cycle	6/9	2,12	0,08
gynecomastia	6/10	1,92	0,07

Source: The authors

Also in our study we got not statistical significance results between dose of Risperidone and score of sexual dysfunction in examination group. (Table 4)

Table 4. Correlations between score of sexual dysfunctions (SD) in examination group and Risperidone therapy

Risperidone/SD	Pearson's correlation coefficient	P level
Libido problems	r= -0,25	0,023
Problems with experiencing orgasm	r=-0,32	0,045
Dissatisfaction of the sexual act	r=0,15	0,034
Dissatisfaction of the overall sexual life	r=-0,32	0,045

Source: The authors

4. DISCUSSION

It is known from the literature that typical antipsychotics have a stronger affinity for D2 receptors, creating more pronounced symptomatology of hyperprolactinemia (Kavarthapu R et al, 2022).

This is not the case with atypical antipsychotics, which have less effect on D2 receptors such as Clozapine, Olanzapine and Quetiapine. However, from this group of drugs, the exception is Risperidone, the use of which leads to an elevated level of prolactin, similar to that with the use of haloperidol (typical antipsychotic) (Amato D et al,2019; Osmanova DZ et all 2019)

Based on this knowledge, the results obtained in our study can be explained. That the symptoms of hyperpolactinemia were represent in a higher percentage in the studied group after treatment with Risperidone tablets.

Different antipsychotic drugs have different effects on serum prolactin levels because some atypical antipsychotic drugs have high affinity for dopamine (D2) receptors such as Risperidone while a group of atypical antipsychotics have low affinity for D2 receptors such as Olanzapine (Amato D et al, 2019; Koch MT et all, 2023)

According to the results obtained in certain studies, i.e. researches, an increase in prolactin in risperidone treatment was observed in 90% versus 50% in patients who were treated with olanzapine. Therefore, it is thinks that replacement therapy with a less potent drug like Olanzapine may be needed .(Osmanova DZ et all, 2019; Özkan HMet all ,2020)

There are also studies that indicate that the expressed symptomatology of hyperalactinemia is much less pronounced in relation to the plasma values of prolactin in the body (Thapa S et all,2023)

On the other hand, it is also possible to have a condition of asymptomatic hyperalactinemia, which condition should not be an indication for a change of medication in itself (Ammari R,et all, 2020)

In this diagnosed state of hyperprolactinemia, the clinical guidelines contained in the protocols of evidence-based medicine must be followed (Kavarthapu R.et all,2022)

Antipsychotics represent a large number of psychotropic drugs that can cause hyperprolactinemia (. Therefore, clinicians must be skilled in stratifying the relative risk of developing hyperprolactinemia as well as recommending therapeutic alternatives and treatment strategies. (Özkan HM et all,2020)

It is generally known that typical antipsychotics compared to atypicals have a higher potency, i.e. a higher probability of raising prolactin, although there are exceptions to the rule (Ammari R et al ,2020; . Kavarthapu R et al, 2022)

If the symptoms of hyperlactinemia appear, it is necessary to reduce the dose or to switch to another, less potent drug such as Olanzapine, Quetiapine, Aripiprazole. And in the end in the last case mast to call an endocrinologist (Osmanova DZ et al,2019; Özkan HM et al,2020)

However, care must be taken not to disturb the heroin addict's mental state. Which situation could lead to his health and social destabilization .(Thapa S et al,2023).

5. CONCLUSION

Although in our study we obtained a small percentage of patients with symptoms of hyperprolactinemia, care must be taken in patients on methadone treatment who are also treated with neuroleptic therapy due to their synergistic effect, we should always keep in mind the possibility of developing hyperprolactinemia. As well as the opportunity to switch to another, less potent drug such as Olanzapine, Quetiapine, Aripiprazole.

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