

CLOZAPINE-INDUCED HYPERSALIVATION TREATED WITH SULPIRIDE - IS IT A SOLUTION?

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INTRODUCTION

Clozapine has emerged as the first treatment option in the case of resistant schizophrenia because various studies have shown it to be more effective than other antipsychotics (Leucht et al. 2014, Azorin et al. 2001). When it comes to patients suffering from schizophrenia who have not achieved a satisfactory response with an atypical antipsychotic, the use of clozapine has been proved to be more effective than the introduction of another antipsychotic (Joseph et al. 2006). Additionally, it has also been shown to significantly improve a patient's overall functioning (Wheeler et al. 2009), and to have a relative advantage over other antipsychotics in curbing aggression in the treatment of resistant cases (Volavka et al. 2002). Clozapine can cause a wide range of side effects, of which hypersalivation is extremely common and can significantly affect a patient's quality of life. The prevalence of excessive sialorrhea ranges between 30-80%, with one study showing a prevalence of 92% (Maher et al. 2016). Clozapine-induced hypersalivation is a common phenomenon whose etiology is not completely clear up to date. It is thought that it increases salivation through activation of muscarinic M4 receptors and/or blockade of Alpha2-adrenergic receptors, or distortion of the swallowing reflex. There are several potential pharmacological options for treating clozapine-induced hypersalivation, such as; anticholinergics, alpha2-adrenergic agonists, or some antipsychotics (sulpiride and amisulpride) that have proved effective in individual studies (Kreinin et al. 2005, Praharaaj et al. 2011). Given that there is not enough research in the literature and case reports on this phenomenon and how it has been handled, we have decided to make our contribution to this quest in seeking a possible solution to this problem.

CASE REPORT

A male patient aged 29, unemployed, unmarried. As an infant of 4 months, he was abandoned by his biological mother. Afterwards, at the age of 6, he began to see her occasionally but their relationship was intense and followed by frequent outburst of anger by the client towards his mother, or on the other spectrum, he would be indifferent when she approached him.

We wanted to briefly emphasize the potential role of early adverse environmental factors and importance of different types of attachments, such as; dismissing & disorganized types. These evolved in the context of relation to his primary caregiver as a predisposing factor in the development of chronic psychotic disorder. From 2001 his biological mother and father have reunited, and they have been living all together. He has been treated since 2009. According to hetero-anamnestic data obtained from parents, the changes on the psychological level occurred in 2008 and were manifested by negative prodromal symptoms with occasional perceptual changes. The first hospitalization followed in 2011 with predominantly negative, aggressive symptoms with an associated executive cognitive dysfunction. After the first hospital treatment, he had been discharged with diagnosis: Unspecified psychotic disorder F29 according to the International Classification of Disease 10th revision (ICD-10). At the first hospital admission, a doctor prescribed him atypical antipsychotic risperidone in amount of 4 mg divided in two daily doses, and clozapine in dose of 2 x 25 mg, primarily for sedative properties.

During the second hospitalization (2012), the patient's diagnosis was altered according to DSM-IV criteria in a Schizophrenic disorder. The main complaints in the second hospitalization and then every subsequent one, were persistent distressed auditory hallucinations, aggression, and fluctuating negative symptoms with impaired cognitive abilities. During the long-term treatment trough last 11 years, the pharmacological therapy was changed several times, one atypical antipsychotic was mainly used with augmentation with a typical highly/low potent antipsychotic. This particular scenario arose in the second (2012) and the third (2017) hospitalization, in which olanzapine in daily dose of 20 mg and haloperidol in dose of 15 mg was applied, then risperidone in dose of 6 mg divided twice daily in conjunction with promazine daily dose of 2 x 50 mg. Due to the inability to alleviate primarily distressed productive symptoms, clozapine, the gold standard in the treatment of resistant schizophrenic disorder (Barns et al. 1996, Remington et al. 2016), has been approached as a last resort at fifth hospitalization in 2018. However, soon after the introduction and titration of the clozapine towards to higher therapeutic doses, side effects occurred in the form of noticeable hypersalivation. Treatment with clozapine discouraged responsible prescribing

physician from continuing to use it, especially with higher daily doses. Throughout the next two hospital treatments which happened at the same year 2018, mood stabilizers at lower therapeutic doses were also used, as an "off-label" adjunctive therapy for the negative symptoms that were observed during these hospitalizations.

The last hospitalization at the Department of Psychiatry followed in March 2020, due to the constantly presented auditory hallucinations to which the patient had reacted with pronounced distress, symptoms of aggression and general dysfunction. Considering the complete course of treatment of the patient, the decision was made again to use clozapine in therapy with gradual titration and active monitoring of efficacy and possible occurrence of side effects.

At the daily dose of 200 mg of clozapine split in two parts, the patient began to report excessive saliva leakage, which was evident by the act of inspection during regular visits to the acute ward of the Department of Psychiatry. However, this time the therapy was not discontinued, but adjuvant therapy with sulpiride was introduced as an "off-label" option in stopping clozapine-induced hypersalivation at the sixth day of therapy. Sulpiride was administered at an initial dose of 2 x 50 mg, while the clozapine dosage was temporarily sustained at 200 mg to monitor the development of the clinical picture. Two psychometric instruments were used during the patient monitoring: A 5-point Nocturnal Scale for Monitoring Hypersalivation (NHRS) and a Scale for Monitoring the Severity and Frequency of Drooling (DSFS).

It was evident already during the first days that the patient reacted with reduced hypersalivation after the introduction of sulpiride, which was an encouragement and an incentive to increase the dose of clozapine according to the therapeutic response. The patient's daily dose of clozapine was titrated over the period of two weeks to 600 mg daily, divided in three daily doses with evening dose of 300 mg. In addition, sulpiride 300 mg was divided in two doses, and top-up usage of haloperidol in dosage of 15 mg was recommended in conjunction with gradual reduction of haloperidol. The therapeutic response to this therapy was satisfactory, with partial lag of distress positive psychotic symptoms and 14-day period without hypersalivation or with minimally present as a trace of saliva on the pillow. On the NHRS scale, which ranges from 0 to 5, this would correspond to 0-1 spectrum, with no daily complaints of saliva leakage, actively monitored and recorded via DSFS.

The patient was discharged from the hospital treatment with satisfactory remission of symptoms from the schizophrenic spectrum, with no side effects associated with clozapine-induced hypersalivation.

However, during subsequent follow-ups, hypersalivation reappeared as a side effect despite regularly taking sulpiride, which initially proved to be an adequate solution for curbing it based on encouraging primary results.

DISCUSSION

In our case report, the main emphasis was placed on the treatment of clozapine induced hypersalivation with sulpiride. The therapy applied at the Department of Psychiatry appeared to be very effective in the short term and went from a gradual reduction to the complete absence of hypersalivation within the first seven days after the application of adjuvant therapy with sulpiride.

Values recorded on NHRS within the first seven days were - 1 (one) until complete cessation of nocturnal hypersalivation, on NHRS - 0 Value of 0 on NHRS was recorded exclusively at lower therapeutic doses of clozapine (200-300 mg). While the dose of clozapine was gradually increased according to the therapeutic response, in the same time, the adjuvant therapy with sulpiride was titrated. Through the rest of hospitalization, a trace of saliva on the pillow was just occasionally observed by a doctor. After the patient was discharged, on the next regular follow-ups the noticeable hypersalivation had again reemerged as a side effect of clozapine treatment, despite of consistent sulpiride intake. In comparison, Kreinin et al. (2005) examined the efficacy of sulpiride in the treatment of hypersalivation and obtained encouraging results. The method of monitoring nocturnal hypersalivation was through observations by both patients and physicians, afterwards recorded on NHRS. In a shorter study lasting 21 days, 18 patients participated, whereby only three patients reported minimal signs of hypersalivation at the end of monitored period. Doses administered to each and every patient differed, with 16 of them being administered 100-300 mg dose of clozapine and 2 of them took 800 mg daily. This translates to absence of correlation of doses prescribed and reduction of saliva leakage, since all patients reported nearly similar results. However, the study did not provide information on long-term effects.

A review of previous studies related to the pharmacological treatment of clozapine-induced hypersalivation has not provided a precise solution to this problem, and has been mainly treated through the putative pathophysiology of hypersalivation (Syed et al. 2008, Chu et al. 2016, Praharaj et al. 2005).

General conclusion cannot be inferred, since the study is pilot-based and greater sample size coupled with potentially longer observatory period might set the ground for more verifiable results. Also, future research is needed regarding the putative pathophysiological mechanism and possible interaction between sulpiride and clozapine primarily at the peripheral level, due to the possible cessation of hypersalivation thereby. Sulpiride is known to reduce gastric acid secretion (Caldara et al. 1983), thus hypersalivation reduction might be attributed to it.

CONCLUSION

The treatment of resistant symptoms complicates the clinical course of schizophrenia, because a large number

of patients do not achieve functional recovery. It is necessary to stress out that the side effects depict serious issue in the therapeutic process, which can discourage the attending physician from continuing with a certain treatment course. As a consequence of this, polypharmacy is often imposed as the only therapeutic option in the treatment of refractory cases. Sulpiride as adjunctive therapy has been shown to be effective in the initial reduction of clozapine-induced hypersalivation, but has not been proved to be satisfactory as the long-term treatment. The effects of sulpiride were evident at lower therapeutic doses of clozapine in terms of complete relief of clozapine-induced hypersalivation (NHRS-0), and at higher doses reduction of hypersalivation was observed as well, (NHRS 0-1). Since the treatment did not maintain initial progress in the long run, the conclusions remain vague, as in the majority of comparable literature.

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Contribution of individual authors:

Emir Prljača: conception and design of the manuscript and interpretation of data, literature searches and analyses, clinical evaluations, manuscript preparation and writing the paper.

Elvir Bećirović: review of literature, consultations and feedback, drafting the final version of article and revising it critically for important intellectual content.

Mevludin Hasanović: review of literature, backstopping consultation, drafting the final version of article and revising it critically for important intellectual content.

Izet Pajević: Backstopping consultation and feedback to the final version of article.

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