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Case Report

Concomitant Use of Antipsychotics and Diuretic Accelerates the Hyponatremia Effect

Nurazah Ismail[1] and Tuti Iryani Mohd Daud[2]

[1]*Psychiatry Unit, Faculty of Medicine and Health Science, Universiti Sains Islam Malaysia, Nilai Negeri Sembilan, Malaysia.*
[2]*Department of Psychological Medicine, Pusat Perubatan Universiti Kebangsaan Malaysia, 56000 Cheras, Malaysia.*

Correspondence should be addressed to:
Tuti Iryani Mohd Daud; tutimd@ppukm.ukm.edu.my

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***Abstract* — We reported a case of severe symptomatic hyponatremia with a serum sodium level of 113 mmol/l after 2 weeks commencement of 2 types atypical antipsychotics; clozapine and amisulpiride with indapamide, a thiazide-like diuretic antihypertensive medication. Discontinuation of indapamide despite of continuation of his antipsychotics showed improvement in his serum sodium level. The aim of our case-report is to emphasize the life-threatening complication associated with the combination of agents that may cause hyponatremia. Both agents are known to cause electrolytes imbalance. Hence, close monitoring of the serum sodium is important during the treatment course.**

***Keywords* — Hyponatremia; Schizophrenia; indapamide; antipsychotics.**

I. INTRODUCTION

Schizophrenia is a chronic relapsing mental disorder that leads to deterioration in social and occupational functioning. It is challenging and difficult to treat. Failure of improvement in the target symptoms (positive symptoms, negative symptoms and cognitive symptoms) despite sufficient dose at 300mg/day equivalent dose of chlorpromazine for at least 8 weeks is considered as treatment resistant schizophrenia (TRS) [1]. Antipsychotic is the mainstay of treatment in Schizophrenia. About 30% of schizophrenia patients will receive the diagnosis of TRS [2]. It is a challenging condition to treat. Majority of cases would use polypharmacy in the treatment of TRS. As a result, it predisposes patients to develop medication-related side effects namely metabolic syndrome which is associated with cardiovascular complications. These will further lead to the additional medications that inclines towards drug-drug interaction. Hence, the benefits versus risks in the treatment of TRS need to be greatly considered.

II. CASE REPORT

Mr. X is a 48-year-old gentleman, presented with changed in behaviors by exhibiting negative symptoms such as social withdrawn, slowness and lack of motivation in his early 20s followed by positive symptoms (predominantly auditory hallucination and persecutory delusion) a year later. He only sought treatment after five years and since then he was diagnosed to have schizophrenia. Due to this, he required multiple psychiatric hospitalizations following aggressive behaviors secondary to commanding auditory hallucination and persecutory delusion that he experienced. He had tried

multiple antipsychotics (risperidone, olanzapine, chlorpromazine, intramuscular (IM) paliperidone monthly) at the optimum dose, at an adequate time, however he still has residual psychotic symptoms. Hence, his diagnosis was revised to TRS in 2015. Tablet clozapine was initiated and titrated slowly according to clozapine protocol until 200mg/day, together with IM paliperidone 150mg monthly and he was able to achieve symptom remission. Later, he was diagnosed with hypertension and calcium channel blocker (amlodipine) was initiated to control his blood pressure. Yet, compliance was an issue and he was presented to emergency department with decompensated cardiac failure secondary to uncontrolled hypertension in October 2017. He was started on diuretic (frusemide), ACE inhibitor (perindopril) and □-blocker (bisoprolol) on top of antipsychotics that he had. Electrocardiograph (ECG) at this point of time was sinus rhythm and his echocardiogram showed ejection fraction of 64% and no regional wall motion abnormality with normal chambers size. Routine blood investigations were within normal range.

In view of adherence issue with his oral medications, he was readmitted again in February 2019. Tablet amisulpiride was commenced till 400mg/day during this admission in addition to clozapine and IM paliperidone. He was planned for electroconvulsive therapy (ECT) but the procedure was cancelled in view of ECG changes (T inversion at II,III, aVF, lead V3-V6). Some of his antihypertensive medications were changed (frusemide perindopril, amlodipine and metoprolol) to control his blood pressure. Nevertheless, he still had residual psychotic symptoms upon discharge.

During his out-patient follow-up, he was psychiatrically well for a year with amisulpiride dosage of 600mg/day, clozapine 175mg/day and IM paliperidone 150mg/month. The medical team had changed his □-blocker to bisoprolol 2.5mg/day and while other medications remained the same.

His admission during this article was written was a year after his last discharged from psychiatric ward in February 2019. At this point of time, in October 2020, he came with similar presentation. In view of his good response with clozapine and it was well tolerated without any side effects in the past, clozapine was reinitiated together with other previous other antipsychotics. While his diuretic was changed to indapamide, while maintaining other antihypertensive medications during this admission. At the time clozapine was optimized to 225mg/day, he developed generalized tonic-clonic seizure secondary to hyponatremia (serum sodium was 113 mmol/L from serum sodium of 130mmol/L). Other investigations including computed topography of the brain were normal. Prior to the event, there was no gastrointestinal loss and his oral intake was good. He required ventilation support and all of his antipsychotics and indapamide were withheld. Subsequently, he was extubated and both clozapine and amisulpiride were resumed. His serum sodium was monitored weekly throughout his stays and it were normal. He was discharged well to the nursing home with clozapine 200mg/day, amisulpiride 600mg/day, metoprolol 50mg twice a day and metformin 500mg twice a day. The summary of his serum sodium as shown in table 1.

III. DISCUSSION

Mr. X had tried multiple types of antipsychotics, both from first and second-generation antipsychotics, but less improvement could be seen in view of multiple relapses. Later, he was put on the combination of both clozapine and amisulpiride (second-generation antipsychotics (SGA)) in which clozapine augmentation with amisulpiride more efficacious compared to clozapine alone towards positive and negative symptoms with less extrapyramidal side effects. Since, metabolic syndromes are more prone among SGAs, [3] he was diagnosed with hypertension and diabetes after he was on these psychotropic medications. Due to his non-adherence towards the medications, he developed the hypertension complications that leads to the additional three antihypertensive medications. Even though his psychopathologies were improving after the combinations of these medications, unfortunately he developed generalized tonic-clonic seizure secondary to severe hyponatremia during his recent acute admission.

There are multiple etiologies that can cause hyponatremia. In this case, it can be explained through the drug-drug interaction between his antihypertensive medications namely Indapamide with antipsychotics which were Clozapine and Amisulpiride. Antipsychotic may cause hyponatremia in the context of water intoxication, drug-induced syndrome of inappropriate antidiuretic hormone (SIADH) and severe hyperlipidemia and/or hyperglycemia [4, 5].

The prevalence of antipsychotic induced hyponatremia was about 10% in a chronic psychiatric patients [6]. Although the information on the risk of hyponatremia is limited, in a systemic review of case reports revealed that clozapine is one of the commonest SGAs that is associated with hyponatremia.

Other SGAs including the -pine group (Asenapine, Olanzapine, Quetiapine), the -done group Risperidone, Paliperidone, Lurasidone, Ziprasidone and Aripiprazole [7]. The risk of developing hyponatremia is three times increased in a patient who did not receive any other concomitant medications that may cause hyponatremia apart from antipsychotics alone [8].

While Indapamide is an antihypertension medication (thiazide-like diuretic) which is a well-known in causing hypokalemia. However, there were many case reports reported indapamide causing hyponatremia as well that is believed to be caused by the indapamide-induced syndrome of inappropriate antidiuretic hormone (SIADH) [9, 10]. Therefore, combination of both indapamide and antipsychotics not only exacerbate the tendency of developing hyponatremia in this patient, but also accelerates the effect of hyponatremia far greater during the first month of its use [11].

TABLE 1. SERIES OF SERUM SODIUM

	Admission 20/10/2020	7/11	8/11	9/11	10/11	11/11	12/11	Discharged 18/12
Serum Sodium (mmol/l)	130	113	118	123	132	135	137	141
Medications	Indapamide was added in while other medications were continued during current admission: Perindopril Bisoprolol Amlodipine Clozapine Amisulpiride IM Paliperidone	Seizure occurrence	All antipsychotics and indapamide were withheld				Restarted patient on amisulpiride and clozapine Indapamide was stopped.	Amisulpiride 600mg/day Clozapine 100mg twice a day Metformin 500mg twice a day Metoprolol 50mg twice a day

*IM= intramuscular

IV. CONCLUSIONS

In conclusion, close monitoring of the electrolytes is vital in psychiatric patients who received antipsychotics especially those with polypharmacy regime as well as among those who has underlying medical co-morbidity with potential medications that can cause electrolyte imbalance to avoid unnecessary adverse drug reaction that may jeopardize patient's life as well as patient's quality of life due to relapses.

CONSENT TO PARTICIPATE

Written informed consent was obtained from the patient for the anonymized information to be published in this article.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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