Quetiapine Related Acute Paralytic Ileus in a Bipolar I Disorder Patient with Successful Low Dose Amisulpride Substitution: A Case Report

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The mechanism of medication-induced gastrointestinal hypomotility is primarily caused by muscarinic cholinergic antagonism. This effect may cause constipation and paralytic ileus, which may lead to fatal complications. A 51-year-old woman was admitted due to manic episode recurrence. She developed paralytic ileus under quetiapine use and treated successfully under low dose amisulpride use. The related mechanism, associated risk factors, and the rationale for medication switch are discussed.

KEY WORDS: Bipolar disorder; Paralytic ileus; Constipation; Quetiapine; Amisulpride; Anticholinergics.

INTRODUCTION

The mechanism of medication-induced gastrointestinal hypomotility is primarily caused by muscarinic cholinergic antagonism. This effect may cause constipation and paralytic ileus, which may lead to fatal complications. Different antipsychotics have different anticholinergic potencies, which should be taken into consideration during medication selection. In this report, we discuss a bipolar I disorder patient who suffered from paralytic ileus and successfully treated without further complication after medication switch to amisulpride use.

CASE

A 51-year-old woman was previously healthy and without personal history of any psychiatric or medical illnesses. Her older sister has bipolar disorder. She has been a pious adherent of Buddhism for more than 15

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episode with psychotic features.

Serial examinations including thyroid function tests were done and no abnormal finding was noted on day 1. We delivered quetiapine 400 mg/day and valproic acid 1,000 mg/day for controlling her manic and psychotic symptoms. We did not use any anticholinergic medication in the entire treatment due to the absence of extrapyramidal symptoms. The valproic acid blood level was 88.94 µg/ml on day 10. Elevated mood was improving with reduced frequency of disturbing behaviors at ward.

On day 15, she complained about abdominal distention and constipation. A kidney, ureter, and bladder (KUB) X-ray revealed focal dilated loops suspecting focal obstruction (Fig. 1A). We delivered cathartics and prokinetic agents with sennoside and domperidone. Sodium phosphate monobasic enema was later performed twice due to limited stool passage. However, aggravated abdominal distention, anorexia, and general weakness were noted on day 17. We tried to taper down quetiapine to 200 mg/day and continued valproic acid use. However, severe abdominal pain and urine retention were found at night on day 17. KUB X-ray revealed gaseous dilatation of the transverse colon and much fecal material retention in colon (Fig. 1B). Nothing by mouth except medication was implemented and decompression with both the anal tube and the nasogastric tube were performed. Quetiapine was also discontinued immediately. The markedly abnormal laboratory findings were leukocytosis with left shift (white blood cells, 10,070/µl; neutrophil, 76%) and a newly-developed hypothyroidism (free thyroxine [T4]: 5.48 pg/ml, thyroid-stimulating hormone [TSH]: 3.09 µU/ml on day 17; compared to free T4: 11.00 pg/ml, TSH: 1.86 µU/ml on day 1). Antithyroglobulin antibody and anti-thyroid peroxidase antibody levels were normal, which revealed no evidence of autoimmune related thyroid disease. Gastroenterology consultation suggested quetiapine related paralytic ileus superimposed with hypothyroidism. Endocrinology consultation also suspected quetiapine related hypothyroidism. Both consultations agreed with our interventions and recommended further observation of her paralytic ileus and thyroid function.

After quetiapine was withheld, her paralytic ileus improved significantly with fair oral intake and stool passage observed the next day. However, manic symptoms with irritable mood and hyper-talkativity exacerbated 2 days after the discontinuation of quetiapine despite the continuous use of valproic acid. We then added amisulpride to 400 mg/day on day 22. KUB X-ray follow-up demonstrated obvious improvement of the paralytic ileus (Fig. 1C). She tolerated well with amisulpride 400 mg/day and valproic acid 1,000 mg/day use and her manic symptoms subsided gradually. We rechecked her thyroid function which revealed improving hypothyroidism status on day 30 (free T4: 7.81 pg/ml, TSH: 3.86 µU/ml). She was later successfully discharged on day 31 under stable condition both mentally and physically.

**DISCUSSION**

The mechanism of medication-induced gastrointestinal hypomotility is primarily muscarinic cholinergic antagonism. Previous study revealed that increasing age, fe-
male gender, treatment with clozapine, high potency first
 generation antipsychotics, tricyclic antidepressants, anti-
 cholinergics and opioids were associated with an in-
 creased risk of ileus. One systematic review study re-
 cently found history of abdominal surgery, longer dura-
 tion of psychiatric disorders, and older age to be risk fac-
 tors of relapse of ileus. Overall, patients treated with an-
tipsychotics had a 1.9 times higher risk to develop con-
stipation compared to non-users. In severe cases, con-
stipation may progress to ileus and bowel ischemia with
multiple fatalities related to sepsis and bowel perfora-
tion. Therefore, we should pay more attention to anti-
psychotic-related constipation and further complications,
such as ileus, to prevent possible fatalities.

Anticholinergic potency differs markedly among anti-
psychotics. Among atypical antipsychotics, clozapine,
olanzapine, and quetiapine have significant affinity for
the muscarinic receptors in vitro, while aripiprazole, ris-
peridone, and ziprasidone do not. Clozapine has the
highest risk for anticholinergic related gastrointestinal ad-
verse effect. One report revealed a patient died from fe-
cal impaction and associated aspiration of feculent vomi-
tus and another patient developed fatal bowel ischemia
within 2 days. Quetiapine was also prone to cause anti-
cholinergic side effects. In the Clinical Antipsychotic
Trials of Intervention Effectiveness (CATIE) study, queti-
apine was found to have significantly more anticholinergic
side effects in phase 1, phase2, and phase 3 trials. Anti-
cholinergic adverse effects had been found in 27% of the
patients treated with quetiapine, and the most common
complaints were dry mouth, urinary hesitancy and con-
stipation. Of note, our patient was antipsychotic-free for
9 months prior to this admission and developed paralytic
ileus within 15 days after quetiapine use, which was
clearly different from the average onset of 3 years after first
antipsychotic prescription reported by Nielsen and
Meyer. However, another case of acute paralytic ileus
within 8 days of risperidone use has also been reported.
Thus, acute onset paralytic ileus related to antipsychotic
use is possible and we should be aware of this and man-
age it promptly if encountered.

As for amisulpride, it is a serotonin dopamine antago-
nist known for its properties of predominantly pre-syn-
aptic D2/D3 dopamine receptor binding and partial D2
agonism. Although not recommended and US Food and
Drug Administration-approved as standard bipolar mania
treatment, it did show good response rate for acute mania
compared to haloperidol in adjunct to divalproex
therapy. Amisulpride monotherapy use in one patients
with bipolar I disorder also showed there may be some
benefits for maintenance treatment of bipolar disorder.
Significant decrease in overall relapse rates, especially
manic episodes, by amisulpride treatment was also found
in one previous study. In addition, no significant anti-
cholinergic properties was associated with amisulpride
and it only possessed minimal risk for constipation com-
pared with other atypical antipsychotics. These were the
main reasons we substituted quetiapine with amisulpride
to control the patient’s manic symptoms and minimized
anticholinergic-related gastrointestinal hypomotility.

The other point worthy of discussion is the relationship
between anticholinergics, hypothyroidism, and the para-
lytic ileus in our patient. Gastrointestinal hypomotility
was known to be associated with hypothyroidism and a
few cases of paralytic ileus associated with hypo-
thyroidism were reported. Furthermore, hypothyroidism
was reported to be an adverse effect of antipsychotics.
Previous study has shown that 0.4% treated with queti-
apine experienced TSH elevations and 60% among them
needed thyroid hormone supplementation. Therefore,
there is a possibility that other than cholinergic antago-
nism, quetiapine may cause paralytic ileus via influencing
thyroid function. However, the logical management
would still be discontinuing quetiapine to reduce its ad-
verse effect on the thyroid gland. Although there is also a
possibility that amisulpride may induce hypothyroidism,
currently only case report has been published. And the
improvement of the hypothyroid state in our patient after
switching from quetiapine to amisulpride did not support
the idea of amisulpride-related hypothyroidism. Currently,
there is insufficient literature determining the potential of
inducing hypothyroidism by various antipsychotics and
further studies are needed in order to guide antipsychotics
use in patients with thyroid dysfunctions.

Considering the prevalence of quetiapine related anti-
cholinergic side effects and quetiapine related hypo-
thyroidism, we suggested that the focus should still be on re-
ducing cholinergic antagonism by discontinuing or
switching antipsychotics when managing paralytic ileus
in bipolar patients to prevent potential fatalities. From the

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well tolerated without anticholinergic side effects and showed good response in treating her manic episode.

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