Multiple extremely overdose of antipsychotics with minimal side effects: A case report

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Title page

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Abstract

Background

Liver cytochrome P450 (CYP450) enzymes play an important role in metabolizing antipsychotics (APs) and other drugs. Excessive use of drugs can impair liver function and even other organs, thus causing several adverse effects. In addition, metabolizer types of CYP450 enzymes may influence the therapeutic effects and drug reactions. In this case report, we introduce a 52-year-old female with a 23-year history of schizophrenia who took overdose of multiple kinds of APs and other herbal preparations together for nearly two years, and she presented with poor treatment effects and minor side effects of APs. This case adds clinical examples for those patients with poor efficacy and alarming drug tolerance.

Case presentation

At admission, the patient showed obviously positive symptoms. She urgently underwent a drug concentration test, and was considered "drug intoxication". She was given an emergency infusion to increase drug excretion. The drug treatment of the patient was adjusted. After pharmacogenomic examination, we found this patient was a CYP1A2 ultra-rapid metabolizer. At discharge, the clinical symptoms of the patient have decreased, and her condition was stable.

Conclusions

CYP1A2 ultra-rapid metabolizer may explain part of the poor therapeutic effects and small adverse effects in this case who took multiple kinds of overdose drugs. Many factors may be involved in the rare presentations in this patient.

Keywords:CYP1A2, ultra-rapid metabolizer, schizophrenia, overdose antipsychotics, side effects

Background

Schizophrenia is a severe mental disorder with heavy burden of comorbidity (1), which make difficulties in the clinical treatment and management of schizophrenia and its comorbidities. The most common therapy for schizophrenia is antipsychotics (APs), most of which are metabolized by the cytochrome P450 (CYP450) system in the liver. Previously, studies had reported that some people can tolerate overdose of APs and this may be explained by pharmacogenetic mechanisms (2). It was found that CYP2D6 ultra-rapid metabolizers were associated with lower risperidone-related adverse events than poor/intermediate metabolizers (3). Therefore, genetic profiling in drug metabolism may help guide clinical treatment in psychiatric diseases (4).

In this case, we described a female patient with schizophrenia who took several kinds of drugs in overdose daily for 2 years, but only slight side effects were observed. This condition attracts our attention and provides some inspiration and reference for the clinical treatment of mental disorders.

Case presentation

The patient is a 52-year-old female with a 23-year history of schizophrenia, aggravated in the last 2 years. She has hypertension, hyperlipidemia, and coronary heart disease. And she is allergic to penicillin. In her family, a maternal aunt has a history of psychiatric disease.

This case first became ill in 1999 (Age 29), with the symptoms of soliloquy, delusion of persecution and reference, and social withdrawal. She was diagnosed of schizophrenia and treated with sulpiride and perphenazine (dosage unknown). The psychotic symptoms were controlled after a month of medication, and the drug regimen was maintained for another 3 months. Then she interrupted medication on her own due to the disappearance of symptoms, and had no recurrence in the next 6 years. In 2006 (Age 36), the symptoms of sensitivity and suspiciousness reappeared, accompanied by headache and abdominal pain. She resumed therapy and her condition improved after treatment with sulpiride and quetiapine (dosage unknown) for a month. Thereafter, she persisted her medication and her condition was stable from 2007 to 2013. From 2014 to 2020, her condition deteriorated twice with the symptoms of delusion of persecution and reference, soliloquy, sensitivity, depression, suicidal ideation, as well as abdominal discomfort and constipation. And she was also diagnosed with hypertension, hyperlipidemia, and coronary heart disease during this period, then she started taking jiangzhining tablets and propranolol (unknown dosage).

Over the following years, she refused to seek medical help and gradually upregulated the dosages of APs on her own by reading package inserts online because of the poor effects of APs on her symptoms. Until 2020, details of the doses she took are given in **Table 1** . Over the next 2 years, she did not adjust her medication regimen. In 2022, she was unresponsive and scatterbrained with delusion of reference and jealousy, hypomnesis, aprosexia, lack of insight, and hypersalivation. To seek further treatment, she was again hospitalized.

The timeline of this case is presented in **Figure 1** .

Clinical Assessment and Therapeutic Intervention

Urgent assessment of serum concentrations of APs at admission was conducted. Serum concentrations of ziprasidone, risperidone, aripiprazole, sulpiride, olanzapine, and clozapine were at 174.34 ng/mL, 62.29 ng/mL, 986.91 ng/mL, 6551.00 ng/mL, 83.78 ng/mL, and 336.52 ng/mL. Physical examination (including blood, urine, stool tests, and head Magnetic Resonance Imaging (MRI)) showed no abnormality, and her vital signs were stable. An electrocardiogram (ECG) showed sinus rhythm, incomplete right bundle branch block, and partial T-wave changes. Admission assessment of psychiatric symptoms showed the existence of delusion, aprosexia, retardation, hypobulia, and lack of insight. The scores of Scale for Assessment of Negative Symptoms (SANS), Scale for Assessment of Positive Symptoms (SAPS), and Treatment Emergent

Symptom Scale (TESS) were 47, 23, and 0. Pharmacogenomic examination is shown in **Supplementary Table 1** .

The patient was diagnosed with "schizophrenia, drug intoxication", an infusion of 2000 ml isotonic solution was given daily to accelerate drug excretion with vital signs were closely monitored. Medication was adjusted to "risperidone 6 mg/day, clozapine 300 mg/day, trihexyphenidyl 4 mg/day, propranolol 20 mg/day, and vitamin complex 3 tablets". Serum concentrations of sulpiride, olanzapine, and aripiprazole decreased to <10 ng/mL, 12.61 ng/mL, and 414.91 ng/mL at the fourth day, and infusion and monitoring was stopped.

Since reducing the dose of medication, clinical symptoms were weekly assessed by clinical scales, the results showed that symptoms did not decrease at the first two weeks. And the patient started to become anxious and worried that her symptoms would worsen. And she had no bowel movements for 3 days. We added sertraline 50mg daily to treat her anxiety, and then the dose was increased to 100 mg/day due to poor effect at the next week. Lactulose oral solution (20 mL/day) was administered for short-term bowel movements.

At discharge, her condition was stable and the medication regime was "risperidone 6 mg/day, clozapine 275 mg/day, sertraline 100 mg/day, trihexyphenidyl 4 mg/day, and propranolol 20 mg/day". Three months later, she came to the clinic for review. Details of drug doses are "risperidone 6 mg/day, clozapine 275 mg/day, sertraline 150 mg/day, trihexyphenidyl l4 mg/day, and propranolol 20 mg/day". The scores of SANS, SAPS, TESS, Hamilton Anxiety Scale (HAMA), and Bech-Rafaelsdn Mania Rating Scale (BMRS) were 18, 4, 4, 14, and 2. Sertraline dose was increased to 175 mg/day for anxiety symptoms.

Discussion and Conclusions

The patient has taken a daily overdose of APs and 2 kinds of herbal preparations for 2 years, but she tolerated these drugs well. We found a CYP1A2 ultra-rapid metabolizer, which may partially explain why side effects were minor in this patient. This case adds to the research evidence of good tolerance for drug overdose in some special populations.

An important concern in this case is that olanzapine and ziprasidone were highly overdosed, but serum concentrations were within or close to therapeutic concentrations. Olanzapine is primarily metabolized by uridine diphosphate-glucuronosyltransferase (UGT) and CYP1A2, and partially metabolized by CYP3A4 (5). Ziprasidone is primarily metabolized by aldehyde oxidase and partially by CYP3A4 and CYP1A2 (5). According to pharmacogenomic analysis, ultra-rapid metabolizer of CYP1A2 may partially explain why twice the recommend maximum dose of oral olanzapine resulted in a nearly normal serum drug concentration.

Another concern of this case was that serum concentration of aripiprazole and sulpiride were highly beyond therapeutic ranges, while she experienced minimal APs-related adverse or toxic effect. And good tolerance observed in this case may benefit from the characteristics of aripiprazole, with partial agonism of D_2 and 5-HT_{1A} receptors and partial antagonism of 5-HT_2 receptors. When taking a daily dose of aripiprazole higher than the recommended maximum dose (30mg), the effect on the serotonergic system was considered to be stronger than the dopamine system because the occupancy at D_2 receptors cannot further increase (6). Thus, a low propensity to extrapyramidal symptoms of aripiprazole was attributed to the partial agonism of D_2 and 5-HT_{1A} receptors, and antagonism of 5-HT_2 receptors was a protective factor for akathisia. As one kind of typical APs, sulpiride has a higher probability to cause extrapyramidal symptoms than atypical APs. A previous study reported that side effects such as hyperprolactinemia and extrapyramidal symptoms increased with D_2 receptor occupancy greater than 72% (7). We hypothesized that 1500 mg sulpiride taken by this patient may not produce a level of D_2occupancy over 72%. This may be one reason for the discrepancy between manifestations and arrestin beta 2 (ARRB2) gene analysis in this case. Unfortunately, we could not obtain the data of D_2receptor occupancy in this case due to technical and conditional limitations.

In this case, poor treatment outcome was observed after the combined use of several kinds of APs. Abnormality or functional changes in the brain may exist in this patient to explain the poor outcome. Changes in dopamine receptor density may be one reason. It was revealed that increasing D_{2L} receptor density could reorient the preferential recruitment of aripiprazole from Gi1 to β-arrestin2 and thus impact the pharmaco-

logical profiles of aripiprazole (8). Another reason may be the activity of the P-glycoprotein (P-gp) drug efflux transporter. Several APs are transportable substrates of P-gp, including aripiprazole, olanzapine, and risperidone. Studies showed that high P-gp activity in schizophrenia induced low therapeutic outcomes, and inhibition or bypassing P-gp activity at the blood-brain barrier (BBB) or intestine may be effective methods to improve the therapeutic efficiency of APs (9).

In general, the metabolic type of CYP450 enzymes, drug-food interaction, receptor density and occupancy, and activity of drug transporter may be related to the poor treatment efficacy and minor side effects of overdose APs in this case.

The reasons for poor therapeutic effects and minor adverse reactions of overdose APs in this case remained inconclusive, CYP1A2 ultra-rapid metabolizer may be one factor. Monitoring drug concentrations of APs and education on rational use of drugs are vital in clinical practice.

List of abbreviations

cytochrome P450 CYP450

APs antipsychotics

MRI Magnetic Resonance Imaging

ECG electrocardiogram

SANS Scale for Assessment of Negative Symptoms

SAPS Scale for Assessment of Positive Symptoms

TESS Treatment Emergent Symptom Scale

HAMA Hamilton Anxiety Scale

BMRS Bech-Rafaelsdn Mania Rating Scale

UGT uridine diphosphate-glucuronosyltransferase

ARRB2 Arrestin beta 2

P-gp P-glycoprotein

BBB blood-brain barrier

Declarations

Ethics approval and consent to participate

This research has been approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (approved number: LYF2023038). Written informed consent was obtained from the patient and her legal guardian for the publication of any potentially identifiable images or data included in this article.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The datasets are available from the corresponding author Dr. LI Zhang (E-mail: *505260@csu.edu.cn*) on reasonable request.

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Authors' contributions

MY wrote the draft of the manuscript. YC collected the case. LZ and HW conceived the article and made multiple revisions to the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figure 1. Timeline of the case

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`Table 1.docx` available at https://authorea.com/users/773697/articles/865565-multiple-extremely-overdose-of-antipsychotics-with-minimal-side-effects-a-case-report