CASE REPORT

Delirium with anticholinergic symptoms after a combination of paliperidone and olanzapine pamoate in a patient known to smoke cannabis: an unfortunate coincidence

Anja Kokalj, Nikolina Rijavec, Rok Tavčar

University Psychiatric Clinic
Ljubljana, Ljubljana, Slovenia

Correspondence to
Anja Kokalj,
anja.kokalj@gmail.com

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SUMMARY

We report a case of delirium with anticholinergic symptoms in a 19-year-old female patient with schizophrenia. On the day the symptoms emerged, the patient received olanzapine long-acting injection and a higher dose of paliperidone. We observed symptoms ranging from confusion to delirium as well as some anticholinergic symptoms. The delirium lasted 24 hours and was managed by intravenous fluid substitution and oral benzodiazepines. Olanzapine pamoate, paliperidone and cannabis are central nervous system (CNS) depressants, and their combination can increase the risks of CNS depression. In this case report, we review the symptoms of delirium in a case of antipsychotic overdose and provide general guidelines for managing these symptoms. We also review possible complications in combined use of cannabis, olanzapine and paliperidone.

BACKGROUND

We highlight the occurrence of a complex syndrome possibly resulting from either an overdose, an adverse effect from an antipsychotic, or accidental application of olanzapine long-acting injection (OLAI). Cannabis overdose is very rare, and its symptoms are very mild, but in combination with other central nervous depressants (eg, antipsychotics) the collective depressive effects could cause more serious complications.

CASE PRESENTATION

A 19-year-old female patient with a diagnosis of paranoid schizophrenia and a known history of using cannabis was regularly treated as an outpatient.

Her first admission to the clinic, in 2011, was due to having experienced suicidal thoughts with a plan, delusions of self-accusation and visual hallucinations. She had tested positive for tetrahydrocannabinol (THC). She also had a history of experimenting with different psychoactive substances such as lysergic acid diethylamide, ecstasy and amphetamines, but in the last year she had mainly been smoking THC. Also, her younger sister was being treated for paranoid schizophrenia. At the time, a complete diagnostic check-up was performed. Physical and neurological examinations, head CT scan, EEG and blood tests showed no abnormalities. Psychological evaluation revealed psychotic symptoms, cognitive disturbances

(thought blocking, problems with concentration and logical thinking) and poor formal thought in comparison to her intellect. She was first prescribed olanzapine in increasing dose to a maximum of 20 mg. She was sedated and still had some religious delusions. Aripiprazole was then added to the olanzapine. The idea behind adding a new antipsychotic was to perform cross-tapering from olanzapine to aripiprazole. During the cross-tapering period, there was no change in psychotic symptoms, but the patient was less sedated. Since she did not respond well to the two antipsychotics, she was offered clozapine, but because of her poor insight and non-compliance she declined and wanted to be discharged. There were no indications of involuntary hospitalisation and she was subsequently treated as an outpatient. From then on, there were no detailed data on how she was treated until her next admission to the clinic, in 2013. As far as we know, she was later switched to paliperidone and OLAI.

Two months before her second admission to the clinic, she received a first dose of OLAI 300 mg; meanwhile, the paliperidone dose was planned to be lowered from 9 mg to 3 mg. On the day of her second admission, her mother accidentally gave her 18 mg (2×9 mg) of paliperidone instead of 6 mg (2×3 mg). Two hours later, she received her fourth dose of OLAI 300 mg, but she already felt tired. The second hour after application of the OLAI, she reported about general malaise. During the third hour she became restless, received bromazepam and went home. Her parents reported that she started hallucinating after arriving home; her psychiatrist later sent her to the hospital.

TREATMENT

At admission she was sedated, restless and confused; her speech was slurred and she was having religious delusions. She was unable to indulge in a conversation. She had tachycardia 120 bpm, but no other physical or neurological abnormalities were detected at the time. ECG was normal. She was involuntarily admitted to the hospital. Owing to the confusion, agitation and damage prevention, and for therapy application, she had to be physically restrained. Vital functions were measured every half an hour and she received intravenous infusions of sodium chloride and glucose. Urine samples showed positive results for THC and

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benzodiazepines, and there was mild leucocytosis in her blood smear.

Nine hours after admission (or 15 hours after 18 mg of paliperidone) she was still delirious and tachycardic, and her body temperature started to increase. It reached 37.7°C. Her skin was hot and dry, and her mouth was dry; the sweating decreased. Her pupils were mildly dilated, with no other neurological abnormalities. The toxicologist suggested continuing monitoring of vital and anticholinergic signs. If there had been signs of urinary retention or bowel obstruction, she would have had to be immediately sent to the emergency unit. As a result of agitation, she received lorazepam, after which she fell asleep for 6 hours.

OUTCOME AND FOLLOW-UP

Twenty-six hours after 18 mg of paliperidone the patient's body temperature and pulse slowly dropped to normal. She was still a little sedated, but could converse. She was not able to say exactly when she had last smoked cannabis. She was discharged from the clinic 48 hours after admission, with neither physical nor neurological abnormalities, but still describing some residual religious delusions.

Currently, ~2 years after these events, she is still being treated with OLAI 300 mg and has agreed to take clozapine 2×50 mg. She responded well to this combination; she now has good insight with no psychotic symptoms.

DISCUSSION

Olanzapine is an atypical antipsychotic that is used in treatment of schizophrenia and bipolar disorder. It is a potent antagonist of serotonergic 2A and 2C, and dopaminergic 1–4 receptors, and has an affinity for muscarinic, histaminic and α -1 adrenergic receptors.¹ OLAI is a depot intramuscular injection of an olanzapine crystalline salt formulation, and can be administered every 2–4 weeks.^{2–3} If the OLAI comes into contact with blood or plasma, a large amount of olanzapine is released into the bloodstream, which can cause postinjection delirium/sedation syndrome (PDSS). This can occur if the needle damages or enters a blood vessel or rich capillary bed.^{2–5} Approximately 91% of PDSS events occur within 1 hour of injection and begin with general malaise, weakness, dizziness or irritability, and then progress to symptoms of delirium or sedation or both. Cases of patients with PDSS have been reported in the literature. Most of them needed only supportive medical care and all recovered in 1.5–72 hours after injection.^{4–5}

Paliperidone is an atypical antipsychotic and an antagonist of dopaminergic 2, serotonergic 2A, histamine 1, α -1 and α -2 adrenergic receptors. It has virtually no affinity with muscarinic 1 receptors.⁶ Paliperidone overdose symptoms may include extrapyramidal symptoms, drowsiness, sedation, QTc prolongation, hypotension and unsteadiness.⁷ There have been several case reports of paliperidone overdose, however, the reported doses in those cases were higher than that in our case.^{8–9} The typical dosing of paliperidone in an adult with schizophrenia is 6 mg/day, and the dose can be increased by 3 mg/day until the maximum dose of 12 mg/day is achieved. After administration of a single tablet of paliperidone, the maximum serum concentration is achieved after 25 hours. Antagonism of histamine 1 receptors can lead to sedation and antagonism of α -1 receptors, and cause orthostasis and tachycardia.⁹

THC is a central nervous system (CNS) depressant with psychomimetic effects together with some peripheral autonomic effects. THC acts on cannabinoid CB₁ receptors.¹⁰ Symptoms of THC overdose are relatively mild, producing drowsiness and

confusion, sedation, intoxication, clumsiness, dizziness, dry mouth and lowered blood pressure or increased heart rate, with no life-threatening respiratory or cardiovascular effects. Even in low doses, THC can produce euphoria and drowsiness sometimes accompanied by sensory distortion and hallucinations.¹¹

The initial symptoms in our case were similar to those in oral olanzapine and paliperidone overdose. They started as general malaise and non-specific symptoms (eg, dizziness, weakness, not feeling well) and continued to worsen to delirium/sedation symptoms. The patient was incapacitated ~7–9 hours after she was given paliperidone 18 mg. She fully recovered 26 hours later.

A high dose of any antipsychotic can have strong anticholinergic effects, which are divided into peripheral and central side effects. Typical peripheral symptoms include: dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate and decreased sweating. Central symptoms include impaired concentration, confusion, attention deficit, memory impairment, excitement and irritability, resulting in hyperactivity and a considerable rise in body temperature, which is accentuated by the lack of sweating.^{12–13} Since antipsychotics have similar receptor profiles, some of the clinical signs can be overlapping. Our patient had general malaise before OLAI was given, which was a consequence of having received a dose of paliperidone 3 times higher than recommended. However, the clinical picture presented during hospitalisation, including high temperature, dry, hot skin, and decreased sweating, was due to the antagonism of muscarinic receptors. In our opinion, this clinical picture could not have resulted from the threefold increase in paliperidone dose, since at the therapeutic dose of 12 mg, paliperidone shows no muscarinic-1 effects.^{6–7–9}

There is no specific antidote for olanzapine or paliperidone overdose. In their literature review, Skomedal *et al*¹⁴ suggest using physostigmine as an antidote. Two case reports of olanzapine overdose with anticholinergic syndrome were published and physostigmine reversed the symptoms almost completely.^{15–16} No further studies were conducted. At present, the guidelines are: symptomatic treatment and monitoring of vital organ function. In some reported cases, pharmacological therapy was used for managing symptoms such as extrapyramidal signs, agitation, elevated blood glucose and hypertension. When using benzodiazepines, we need to be alert for excessive sedation and cardiorespiratory depression. In cases of circulatory collapse or hypotension, intravenous fluids and/or sympathomimetic agents can be applied.¹⁷ In our case, all proper procedures were followed.

In the literature, there are no known cases of interactions between olanzapine, paliperidone and cannabis; however, an anticholinergic effect of cannabis was reported recently.¹⁸ CNS depressants (eg, THC) may enhance adverse/toxic effects of other CNS depressants (eg, olanzapine and paliperidone). Such effects may include, but are not limited to: ataxia, confusion, drowsiness, respiratory depression, weakness, agitation and other signs of delirium, including hallucinations, termed as sensory disturbance in cases of THC overdose. As a result of the THC effect, delusions and other perceptual disturbances were pronounced in this case, but we did not obtain information on the amount and temporal sequence of cannabis consumption since the patient denied its use.

In Slovenia, the Mental Health Act strictly defines indications for exceeding the maximum doses of antipsychotics. The maximum dose can be exceeded when no other effective treatment method is available, when it is absolutely necessary for

effective treatment, and if the patient has given written consent. When all three criteria are met, at least three independent doctors have to be consulted and give their approval for exceeding the maximum dose.¹⁹ Olanzapine was a first-choice antipsychotic in our patient, but despite the maximum dose, some psychotic symptoms persisted. Given that the criteria for exceeding the maximum dose were not met, cross-tapering of two antipsychotics was performed. During the period of cross-tapering, the patient expressed her wish to be discharged and hence the cross-tapering had to be stopped. The patient strictly declined clozapine for a long time and probably, to achieve better compliance, a depot dose of olanzapine was given. Polypharmacy can represent a potential threat for additive adverse effects of antipsychotics, but because of our legislation, it is unavoidable most of the time.

This case report has some major limitations. The first limitation is the poor data on the reasons for continuation of polypharmacy in an outpatient setting. Second, the information about cannabis consumption is insufficient. We only have a THC-positive urine test, which means that cannabis could have been consumed at any point in the 2 weeks before the admission to the clinic. Furthermore, this case would be more instructive if measurements of plasma concentration of both antipsychotic and THC were taken.

Nevertheless, we feel confident in reporting a case showing an occurrence of a complex syndrome most likely resulting from an additive adverse effects of two or more antipsychotics, antipsychotic overdose, or accidental application of OLAI, and its management.

Learning points

- High doses of antipsychotics or additive adverse effects of antipsychotics can cause delirium with anticholinergic symptoms.
- Treatment is symptomatic, however, there are two case reports where physostigmine was used to reverse anticholinergic symptoms in an olanzapine overdose.^{14–16}
- Cannabis may enhance toxic effects of antipsychotics on the central nervous system.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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