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Case Report

Loperamide overdose-induced catatonia: potential role of brain opioid system and P-glycoprotein

Di Rosa E, Di Rosa A.E. Loperamide overdose-induced catatonia: potential role of brain opioid system and P-glycoprotein

Objective: Catatonic features are observed in several psychiatric illnesses but can also be found following substance misuse. Loperamide is an anti-diarrhoeal medication that acts on opioid receptors in the intestine, reducing peristalsis. It is normally unable to pass through the intestinal wall or the blood–brain barrier; however, high dosages can in fact induce the effects on the central nervous system.
Case report: We describe the case of a 20-year-old man who presented with severe catatonia following excessive intake of loperamide, fully remitted with lorazepam.
Conclusion: We speculate on a possible increase of loperamide's bioavailability after overdose owing to reduced expression and functioning of P-glycoprotein.

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Background

Catatonic features are common findings in a variety of psychiatric disorders and medical conditions as a consequence of discrete nervous system impairment related to neurotransmitter interference (1).

Catatonia classically characterises as a subtype of schizophrenia but can also occur in patients with affective psychoses or severe metabolic disorders. On the other hand, literature describes the occurrence of catatonic manifestations following abuse of illicit substances or prescription drugs, which are among the ones acting on opioid receptors in the central nervous system (CNS) (2). However, catatonia has also been correlated to other receptor system interaction: dopaminergic, serotonergic, glutamatergic and gabaergic (3). Therefore, catatonia can be considered a psychopathological behavioural model, depending on several causes, which the Diagnostic and Satistical Manual (DSM-IV) describes as: motor immobility, catalepsy or stupor; excessive motor activity; negativism or mutism; inappropriate or bizzarre postures; and echolalia or echopraxia (4).

Loperamide is a drug licenced to control diarrhoea (5). It is a phenylpiperidine derivative with an agonist effect on the opiate receptors in reducing bowel peristalsis, and it is an avid substrate for P-glycoprotein (P-g), a multidrug efflux transporter that prevents drug substrates from crossing the blood–brain barrier (BBB) (6). The assumption of high doses of loperamide to reduce stubborn diarrhoea or with suicidal intent also results in the effects in the CNS reversed by naloxone (7), a central opioid receptor antagonist. The pathogenetic relationship of brain opioid receptors, for example, in the thalamus, limbic system and brain cortex, and the development of catatonia are reported by some authors describing adverse events following intake of opioids or drugs alike (8).

Case presentation

We describe the case of a 20-year-old man with regular birth and child development, a final-year student at a technical school, with no history of child or adolescent physical illnesses or traumas. At 13 years of age, he reported episodes of fleeting overvalued ideas of omnipotence when drinking alcohol. At 15 he used to spend most of his spare time using computer, hence restricting his social life to a great extent. At 16 he failed to pass to the upper school year because he felt tired, miserable, powerless, abulic and sad. He also suffered from a quasi-hypochondriac worry for a sacrococcygeal fistula, which was then resolved surgically. After a few months, this seemed all sorted with no pharmacological or psychological intervention. Between 17 and 20 years of age, he returned to a fulfilling social life and was able to comply with his academic duties with good marks at school each year up to the completion of his high school grade. Recently, he had not abused substances or alcohol and smoked 10 cigarettes daily.

Roughly 20 days before starting his final exams at school, he presented with nausea, vomit, abdominal cramps and diarrhoea many times a day. As recommended by his general practitioner, he took loperamide 2 mg three times over 6 h time with full remission of symptoms. However, through the following days, he felt tired, poorly motivated or active and unwilling to study. On the night preceding the first session of his exams, he suffered again with a number of diarrhoeal evacuations with stomach cramps, which he treated with three tablets of loperamide 2 mg over 6 h, managing to reduce symptoms. In the morning, he felt 'weird', confused and drowsy but managed to make an effort and attend the exam. In the evening and at night, the painful diarrhoea reappeared. Our patient was looking forward to resolving this with more tablets of loperamide because he was afraid to be unable to attend the second session of his exams the following morning. He then took up to six tablets of loperamide 2 mg during the night. In the morning, he was found confused and miserable, not able to attend his exams. His general practitioner suggested to take him to the hospital where he was assessed with delirium and severe motor retardation. He was tested negative for alcohol or substances of abuse. He disclosed having suffered diarrhoeal symptomatology and used nine tablets of loperamide 2 mg in the previous 30 h, of which he took six tablets in the last 12 h. He was given naloxone (0.4 mg, i.v.), an opioid antagonist suggested for loperamide overdose. Symptoms were attenuated and the patient was discharged home. Subsequently, he again displayed stupor, mutism, motor retardation, negativism, refusing to eat or drink, and self-care. He was constipated and had difficulty in urinating. He was seen in an outpatient assessment and was prescribed olanzapine 10 mg/day, which he took only for 2 days when the symptomatology worsened with immobility and negativism. He was therefore admitted to our ward where stupor, mutism, negativism, generalised increased muscle tone, waxy flexibility, catalepsy, sweating and urinary retention were observed. Brain, heart, kidney, liver conditions and blood parameters were normal. He was treated with saline and glucosate solutions, and lorazepam 7.5 mg/day (2.5 mg, three times) was administered orally.

In the next few days, we observed a consistent reduction in the symptoms and increase in initiative, spontaneous motor functioning, and food and fluid intake, with the patient finally achieving full remission and returning to normal state. He was discharged fully remitted and with lorazepam reduced to 1 mg three times daily, which he took for further 6 weeks, according to the instructions. On follow-up over the phone a few months after discharge, the patient reported full recovery and achievement of academic goals as planned.

Discussion

Catatonia is a psychomotor syndrome observed in a variety of psychopathological conditions: schizophrenia, schizophreniform disorder, brief psychosis and mood disorders. It is also correlated to drug effects on different receptors in the CNS. Literature describes catatonic signs following administration of opioid receptor agonists (1,8). This might suggest that our patient took excessive amounts of loperamide, which ended up passing the BBB interacting with central opioid receptors, also favoured by a higher level of substrate than what P-g was able to keep out of the BBB. The increased bioavailability of loperamide facilitated its effects. However, Vandenbossche et al. consider the literature evidence insufficient to support this mechanism when loperamide is taken at the recommended dose (9).

Reduced bowel peristalsis might have contributed to increasing the quantity of substance absorbed. Moreover, medical intervention was confined to a single naloxone administration without gastric lavage or activated charcoal that could have helped reducing intestinal amounts of loperamide (10). Naloxone was able to resolve the catatonic state only for a short time, possibly because of its short half-life (1–2 h) as opposed to loperamide's which is eight times as long. Olanzapine 10 mg/day was administered for 2 days only and did not seem likely to contribute to a catatonic exacerbation, although this cannot be

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completely ruled out. Conversely, catatonic features remitted in a few days' time during treatment with lorazepam, well known to be effective for this syndrome (11).

We did not perform any head scan. Of the opioid drugs, meperidine is known to induce irritative effects on the CNS, producing psychiatric symptoms including catatonia; in addition, severe brain damage has been described following opioid overdose. However, in our patient, benign outcome and positive response to lorazepam excluded toxic brain damage from opioid overdose (12,13).

It should be taken into account that subjects who experienced catatonia following opiate administration had suffered from various psychopathological episodes in the past, such as the 20-year-old man described here. This might suggest that some unknown biological factor could influence both mental vulnerability and catatonic susceptibility, possibly along with poor efficiency of P-g expression.

Conclusions

We are not aware of any other reports in the literature describing catatonia after loperamide overdose. Our case report with loperamide can be added to a few others in the literature reporting similar reactions from other opiates. This encourages us to recommend to carefully investigate subjects who presented with catatonia on possible previous administration of high doses of opiates such as loperamide. Limitations of this case might be the lack of a comparative scale for catatonia. Nevertheless, this would go beyond our aims of case description, which intended to make a comparison between separate time periods on the basis of clinical observation.

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Disclosure

No conflicts of interest to declare. This article is an original paper, not submitted currently to any other journal for publication.

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