

Loperamide and P-glycoprotein modulator in opioid detoxification

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Opioids contribute to 70% of the negative health impact associated with drug use disorders. A new opioid withdrawal protocol using over-the-counter medications loperamide and P-glycoprotein inhibitor (omeprazole) was described by Dr Al Garhy previously. In this article the successful use of this protocol, evidenced by the Clinical Opiate Withdrawal Scale, is discussed in a case series.

In 2015, 29.5 million people around the world suffered from drug use disorders; opioids contributed to 70% of the negative health impact associated with drug use disorders, and were considered to be the most harmful substances of abuse.¹ According to DSM-5 diagnostic criteria, opioid withdrawal syndrome is defined as: 'Three or more symptoms, developing within minutes to several days of ceasing or reducing opioid use that has been heavy and prolonged or administration of an antagonist after a period of opioid use'. Withdrawal symptoms might include nausea, diarrhoea, fever, muscle aches or insomnia.²

The focus for any opioid detoxification protocol is to complete the process in a prudent, pragmatic and productive manner. In health care settings, opioid detoxification classic approaches include the use of opioid agonists (eg methadone), partial agonists (eg buprenorphine), non-opioid

Table 1. Patient diagnoses, COWS scores and additional treatment for withdrawal

Patient	Diagnoses according to DSM-5	COWS score on admission before treatment	COWS score 2–3 days after starting treatment	COWS score on discharge	Additional treatment besides loperamide and omeprazole
1	Opioids withdrawal Cannabis use disorder	0	7	0	Quetiapine 50mg Zopiclone 7.5mg
2	Opioids withdrawal Stimulant use disorder Sedative use disorder	2	1	1	Quetiapine 200mg
3	Opioids withdrawal	1	12	1	Quetiapine 100mg Lorazepam 1mg 3 times daily
4	Opioids withdrawal Stimulant use disorder Sedatives use disorder Cannabis use disorder	3	1	0	Quetiapine 200mg Escitalopram 30mg
5	Opioids withdrawal Stimulant use disorder Sedatives withdrawal Cannabis use disorder	6	5	0	Chlordiazepoxide 20mg 3 times daily

Abbreviations: COWS: Clinical Opiate Withdrawal Scale

alternatives (eg α 2-adrenergic agonists such as clonidine) or sometimes symptomatic medications (eg loperamide for diarrhoea).^{3,4}

One of the most widely used scales to objectively measure the severity of opioid withdrawal symptoms and the response to withdrawal treatment is the Clinical Opiate Withdrawal Scale (COWS). It assesses both signs and symptoms of withdrawal. Items include anxiety or irritability, gastrointestinal upset, restlessness, bone or joint aches, sweating, rhinorrhoea, tremor, gooseflesh, yawning, pupil size and pulse rate.⁵

A new opioid withdrawal protocol using over-the-counter

medications loperamide and P-glycoprotein inhibitor (omeprazole) was suggested by the primary author in 2014, after proved effectiveness in 44 patients undergoing opioid withdrawal.⁶ The study examined some of the safety and effectiveness measures such as length of stay, side-effects and patients' demands to increase treatment dosage, but no scales were used to assess severity of withdrawal manifestations.

In this context we will present data from a series of five cases admitted for opioid withdrawal management in the same unit (see Table 1). Loperamide and P-glycoprotein inhibitor (omeprazole)

were used for opioid withdrawal management and COWS was used to assess withdrawal symptoms severity on a daily basis, during the course of admission.

Case 1

This case refers to a 35-year-old married man, of Arab ethnicity, working in a regular office job, who was admitted to the substance misuse inpatient unit through the outpatient clinic within the same facility. The patient initially had no complaints; he was keen to be admitted to the inpatient detoxification service. He had a history of increasing use of cannabis and opioids – mainly morphine intravenously, up to 5mg daily – continuously for the past three months. There was no significant history of other mental health disorders or alcohol misuse. He was prescribed quetiapine 50mg at bedtime for insomnia in another psychiatric facility before admission to manage his sleep problems. Mental state examination and neurological examination, on admission, were unremarkable. Blood work up results and electrocardiogram were insignificant.

On the day of admission, COWS total score was 0 (no withdrawal), as he had had the last dose of morphine the same morning. The initial treatment regimen administered included omeprazole 20mg twice daily, loperamide 2mg three times daily, and his 50mg quetiapine at bedtime, as prophylactic treatment for anticipated withdrawal symptoms.

Two days after admission, the patient reported having generalised body aches, chills and sweating, diarrhoea and difficulty sleeping. COWS total score was 7 (mild withdrawal). Zopiclone 7.5mg as needed was added to help with the occasional insomnia

with no increase in the doses of the previously added medications. Withdrawal symptoms were improving gradually. Eight days after admission, COWS total score was 0 (no withdrawal). He was discharged home after completion of detoxification with a plan to evaluate him every week in the outpatient department. He was seen twice after discharge and reported to be still abstinent.

Case 2

A married, unemployed, 27-year-old man, was admitted to the substance misuse inpatient unit through the outpatient clinic within the same facility for a short-term detoxification program. The patient, who was self-referred, reported a three year history of polysubstance misuse. He was administering heroin intravenously, up to 1g daily, along with methamphetamine intravenously. In addition to that, he was abusing benzodiazepines (mainly alprazolam, clonazepam and diazepam), orally, continuously for the same time period. He used to smoke two joints of cannabis daily for three years as well. His last dose of all mentioned substances was three days prior to admission. The patient reported using quetiapine 200mg for his sleep disturbances, which was prescribed to him from another clinic. There is no significant history of medical or other psychiatric disorders. He was admitted for rehabilitation in three different facilities, one of them being mandated by a court order aimed at compulsory rehabilitation for a period of four months. Mental state examination on admission was unremarkable.

On the day of admission, COWS total score was 2 (no withdrawal). Routine blood workup was ordered along with electrocardiogram,

which were all revealed to be unremarkable. The initial treatment regimen comprised of quetiapine 200mg, omeprazole 20mg twice daily, and loperamide 2mg three times daily. On day 3 of his inpatient stay, the COWS total score was 1 (no withdrawal). On day 5, the COWS total score was 1 (no withdrawal). The patient did not have any complaints nor any signs of withdrawal throughout his hospital stay. He was discharged home after completing the detoxification course, on quetiapine 200mg with a plan to visit the outpatient department weekly, but he did not show up.

Case 3

This case refers to a 35-year-old single man, who had admitted himself voluntarily to the substance misuse inpatient unit through the outpatient clinic within the same facility. He had a two-year history of increasing use of opioids. He was using morphine intravenously, up to 1.5mg daily for the past two years. At the time of evaluation he was complaining of interrupted sleep and mild anxiety. His last dose of morphine was on the same morning of admission. He did not have significant history of medical or other psychiatric disorders. Mental state examination and neurological examination were unremarkable.

On the day of admission, COWS total score was 1 (no withdrawal). The initial treatment regimen included quetiapine 100mg at bedtime, lorazepam 1mg three times daily, omeprazole 20mg twice daily, and loperamide 2mg three times daily. On day 2 COWS total score was 12 (mild withdrawal). He was complaining of generalised body ache, vomiting and diarrhoea. Medications were continued at the same doses and

the patient was examined frequently. On day 7 COWS total score was 1 (no withdrawal) and he was discharged home on quetiapine 100mg at bedtime. The discharge plan was to assess him every week in the clinic. He was seen three times after discharge and reported to be still abstinent.

Case 4

This case refers to a 29-year-old married man who had lost his job in the police due to his substance misuse problem. The patient presented to outpatient clinic voluntarily asking for admission to the substance misuse unit for substance detoxification. He had a history of polysubstance misuse. He was injecting heroin, intravenously, up to 1g daily for the past three years, along with abusing methamphetamine, cannabis and benzodiazepines for the same period. At the time of evaluation, he did not have any complaints of withdrawal-like symptoms or intoxication. His last doses of all mentioned drugs were three days before admission. He did not have a significant history of medical or other psychiatric disorders. Mental state examination and neurological examination were unremarkable.

On the day of admission, COWS total score was 3 (no withdrawal). The initial treatment regimen included quetiapine 200mg at bedtime, escitalopram 30mg once daily (his regular treatments before admission), omeprazole 20mg twice daily, and loperamide 2mg three times daily. On day 2 COWS total score was 1 (mild withdrawal). The patient did not develop any withdrawal symptoms during admission, but he did not seem to be motivated to continue the detoxification program. He was discharged on day 3 when his

COWS total score was still 1 (no withdrawal). The discharge plan was to visit the outpatient clinic weekly. He never showed up for his appointments.

Case 5

A single 24-year-old unemployed man, who was transferred to substance misuse unit from acute internal medicine unit after being admitted for opioid and benzodiazepines intoxication. He used morphine intravenously, up to 0.5mg daily, for the previous four years, along with amphetamine injections, cannabis, benzodiazepines and pregabalin in high doses for almost the same duration.

On admission he complained of interrupted sleep, anxiety, low mood and fatigue, but had stable vital signs. He did not have any significant history of medical or other psychiatric disorders. Forensic history was significant with two periods of imprisonment for illegal use of substances. Mental state examination and neurological examination were unremarkable.

On the day of admission COWS total score was 6 (mild withdrawal – he had insomnia and anxiety). The initial treatment regimen included omeprazole 20mg twice daily, loperamide 2mg three times daily and chlordiazepoxide 20mg three times daily. On day 3 COWS total score was 5 (mild withdrawal). The patient did not report worsening of withdrawal symptoms. On day 5 omeprazole and loperamide were discontinued as the patient reported no withdrawal symptoms. Chlordiazepoxide was reduced gradually to 10mg twice daily. On day 7 COWS total score was 1 (no withdrawal) and he was discharged with a plan to follow up weekly in the clinic. He

did not show for his clinic appointments.

Discussion

This case series is to further highlight the effectiveness of opioid detoxification using loperamide and P-glycoprotein modulator. Whereas the withdrawal process for opioids is seldom life threatening in comparison with that for alcohol owing to the likelihood for seizures and delirium, the physical uneasiness renders it difficult to tolerate.⁷

Loperamide is a P-glycoprotein substrate, which is a cheap, widely available, over-the-counter drug that acts primarily in the gastrointestinal tissues to treat diarrhoea. It was reported that if used in larger than recommended doses it can penetrate the blood brain barrier and have methadone-like effect. Furthermore, it has been reported that loperamide has been used among users of opioids to manage opioids discontinuation symptoms.⁸ Loperamide is a phenylpiperidine derivative and μ -opioid receptor agonist, does not readily cross the blood-brain barrier and thus has minimal impact on the central nervous system. As it is a P-glycoprotein substrate, co-administering it with a P-glycoprotein inhibitor such as omeprazole (a proton pump inhibitor) would support breaching this barrier, converting it from a peripherally-acting μ -opioid receptor agonist to treat diarrhoea to a central-acting opioid agonist that reduces the full spectrum of opioid withdrawal manifestations.⁹ The effectiveness of loperamide and omeprazole as part of an opioid detoxification protocol was examined in a retrospective study, published in 2014, by the primary author.⁶ The study had

examined patients' characteristics and treatment outcomes of 44 patients admitted for opioid detoxification in a substance misuse inpatient unit in a tertiary hospital, in Abu Dhabi, UAE, over a two year period. Length of stay, serious adverse events, side-effects and 'requested increased doses of protocol medication' were measured in the study. The mean length of stay was 18.96 days. No side-effects or serious adverse events were associated with the protocol and no requests for an increase in the doses of loperamide or omeprazole were recorded. The above mentioned protocol uses a dose of loperamide that is less than the maximum FDA approved dose¹⁰ hence no adverse events were anticipated, nor reported by patients.

The five cases described in this paper were detoxified using the same protocol comprising loperamide and omeprazole. Effectiveness was measured using the Clinical Opiate Withdrawal Scale (COWS) to quantify opioid withdrawal symptom intensity. One of the important aspects of administering an opioid withdrawal scale is its ability to distinguish between the presence and absence of withdrawal, which is ensured by the COWS as evidenced by its high internal consistency.¹¹ Four out of the five patients were initially admitted with no withdrawal symptoms as the last dose of opioids intake was less than three days prior to admission while the fifth patient was admitted with mild withdrawal symptoms with the COWS recording a score of 6. Patient numbers one and three developed mild withdrawal symptoms (COWS score of 7 and 12 on day 3 and day 2, respectively), and there was an absence of withdrawal symptoms on Day 7 (COWS score of 0, on day 8 and

7, respectively). On the other hand, patient number two had not complained of any withdrawal symptoms (COWS score of 1 on day 1 and day 5 – discharge day). Although patient number four had also not exhibited any withdrawal symptoms (COWS score of 3 and 1 on day 1 and day 2 respectively), they did not complete the rehabilitation program and left the hospital by day 3 (COWS score of 1 on discharge). The fifth patient showed improvement in withdrawal symptoms (COWS score of 5 on day 3) followed by no withdrawal (COWS score 1 by day 7 on discharge).

Four patients had received small doses of quetiapine, which is an antipsychotic medication, whereas patient number five received another antipsychotic – olanzapine – in addition to the detoxification protocol, for the management of insomnia. While having an understanding that quetiapine may have long-term side-effects, these may be overlooked when compared with the short-term abuse of benzodiazepines.¹²

Conclusion

This case series shows that an opioid detoxification protocol using a combination of loperamide and omeprazole is effective, as evidenced objectively by application of the Clinical Opiate Withdrawal Scale. The five patients reported in the paper showed no or mild withdrawal symptoms and four were discharged after seven days of hospital admission (one patient did not complete the rehabilitation program). Further studies are necessitated to expand on the loperamide and P-glycoprotein modulator complex to substantiate the results of this case series.

Declaration of interests:

No conflicts of interest were declared.

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