Psychiatry Research Case Reports 1 (2022) 100070

Contents lists available at ScienceDirect

Psychiatry Research Case Reports

journal homepage: www.elsevier.com/locate/psycr

Clozapine-induced diarrhoea: A case report of an unusual adverse reaction

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ARTICLE INFO

Keywords:
Clozapine
Rare
Adverse
Reaction
Diarrhoea

ABSTRACT

Clozapine has proven efficacy in treatment-resistant schizophrenia, though there have been reports of untoward reactions to its use, including cases of rare side effects. The authors here describe a case of an unusual constellation of symptoms, predominantly diarrhoea, that consistently occurred over 3 attempts to treat a patient with clozapine. We conclude with a recommendation that clinicians need to be aware that new-onset diarrhoea may be an adverse reaction to clozapine.

Introduction

1.1 Clozapine is an atypical antipsychotic recommended for treatment-resistant schizophrenia (Lally et al., 2016). defined as a failure to respond adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs, at least one of which should be a non-clozapine second-generation antipsychotic. (National Institute for Health and Care Excellence, 2021) It has been shown to cause an improvement in symptoms in at least 30% of patients who met criteria for treatment-resistance (Kane et al., 1988). This effectiveness has meant that clozapine is being increasingly prescribed, though not recommended as a first-line drug (Bachmann et al., 2017). Unfortunately, despite its beneficial effects, it is also associated with significant adverse effects, including sialorrhea, agranulocytosis, myocarditis, constipation, seizures, metabolic side effects, and infections, any of which may sometimes limit the use of clozapine (Haidary and Padhy, 2021, Mace et al., 2022 Jan 7). Importantly, other less reported untoward effects of clozapine which may also limit its use, have been identified, including pulmonary thromboembolism, periorbital oedema, priapism and urinary incontinence, acute generalized exanthematous reactions, including Stevens-Johnson syndrome, and diarrhoea/abdominal distension (De Fazio et al., 2015).

We here describe the case of a patient who consistently reacted to clozapine prescription very early in her treatment, and at very small doses, with a constellation of fever, abdominal pain, and diarrhoea.

Case report

2.1 The patient had a diagnosis of schizoaffective disorder and harmful use of multiple illicit psychoactive substances, including cannabis, cocaine, and ecstasy. At the point of admission, there was a history of 5 previous admissions to a psychiatric unit, with the latest lasting nearly 4 years, with the last 3 spent on a locked rehabilitation unit. During these admissions a number of antipsychotics were tried including two short clozapine trials.

2.2 The patient was first considered for clozapine whilst in hospital for the third time, having remained manic, irritable, delusional, and thought-disordered on amisulpride, followed by a combination of 3 antipsychotics. The managing team commenced clozapine with the patient's consent. ECG and white cell counts were normal, and the first dose of clozapine was administered. Five hours after, there was a transient drop in diastolic blood pressure, but it was thought safe to continue clozapine as blood pressure was still within normal range. Three days later, there was a tachycardia of 104, nausea and drowsiness but clozapine was continued. Clozapine titration continued over the next week without incident. On day 7, with clozapine at a dose of 50mg, the patient was noted to have low blood pressure of 89/60 lying compared to 114/81 standing. The patient also reported bowel movements on that day after previously being constipated. As the patient still reported subjected wellness, clozapine was continued. Eight days into clozapine, it

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https://doi.org/10.1016/j.psycr.2022.100070
Received 22 July 2022; Received in revised form 4 October 2022; Accepted 7 October 2022

Table 1
Blood tests

Parameter	Baseline tests for 2nd clozapine trial	Day 4, 2nd clozapine trial	6th day post-discontinuation of clozapine in 2nd trial	Baseline tests for 3rd clozapine trial	Day 4, 3rd clozapine trial
White Cell Count [4 - 11 10^9/L]	7.12	8.12	9.75	7.45	6.5
Red Cell Count [3.8 - 5.8 10^12/L]	4.58	4.76	4.74	4.87	4.28
Haemoglobin [115 - 155 g/L]	138	142	142	147	126
HCT (PCV) [0.37 - 0.47 L/L]	0.4	0.42	0.43	0.425	*0.367*
MCV [77 - 100 fL]	87.3	88.2	90.7	87.3	85.7
MCH [25 - 34 pg]	30.1	29.8	30	30.2	29.4
MCHC [304 - 360 g/L]	345	338	330	346	343
Platelet Count [150 - 450 10^9/L]	214	168	204	195	158
Mean Platelet Volume [9.1 - 12.8 fL]	9.8	10.2	9.3	10	9.9
Neutrophils [1.5 - 6.3 10^9/L]	4.03	5.52	5.1	3.68	2.98
Lymphocytes [1.3 - 4 10^9/L]	2.28	1.65	3.52	2.83	2.45
Monocytes [0.2 - 1 10^9/L]	0.56	0.82	0.80	0.59	0.59
Eosinophils [0 - 0.4 10^9/L]	0.22	0.12	0.29	0.31	*0.44*
Basophils [0 - 0.1 10^9/L]	0.03	0.01	0.04	0.04	0.03
CRP (mg/L)	13	96	10	-	93
Troponin	<3	<3	<3	-	-

was noted that the patient had become 'far less chaotic with no pressured speech or bizarre ideation'. It is of note that bowel movements were recorded as 'normal' at this point, though the patient had been prescribed lactulose for the constipation reported 2 days earlier. By day 10 of clozapine initiation and at a dose of 100mg, the patient reported 'coming down with something' and described stomach-ache and faecal incontinence, and by the next day, was in a poor state, being anorexic, nauseous, vomiting, pyretic with a temperature of 38.2C, and complaining of right lower abdominal pain. The patient was transferred to a medical ward. Though the patient suspected the symptoms were related to the clozapine, medical specialists initially thought of gastroenteritis or appendicitis and an abdominal ultrasound scan and stool test was requested. The report of the blood tests is replicated in column 1, Table 1.

By day 13, the patient declined further clozapine, attributing the physical symptoms to the medication. An abdominal scan on day 14 returned normal. The patient settled out over the following two days and was not re-commenced on clozapine on that admission.

2.3 The patient did not remain well in the community and was hospitalised. From the outset, the new managing team working on the premise of previously reported side effects to clozapine but noting that clozapine remained the best chance of remission of symptoms, decided on a slow titration with careful monitoring of side effects. The team's strategy for trial of clozapine included supporting the patient to quit smoking, starting a stool chart, pre-clozapine initiation blood tests to include FBC, HbA1c, CRP; starting antiemetics and Gaviscon (a laxative) with clozapine initiation and gradually discontinuing other antipsychotics when clozapine commenced. The patient again consented to clozapine after being reassured of measures being taken regarding potential side effects when the patient expressed worries as per previous gastrointestinal reaction.

2.4 All blood reports at clozapine initiation showed normal values except for deranged lipids, isolated low T4 (sick euthyroid), and a borderline raised CRP of 13mg/L (Table 1). The team commenced clozapine with a single dose of 6.25mg on day 1. Other medications that were prescribed at the time of commencing the patient on clozapine are shown in Table 3. By the next day, the patient reported crampy lower abdominal pain initially thought to be dysmenorrhea. The team also thought it was too early to associate a single low dose to clozapine-induced constipation as the patient had not passed stool. Later the same day, there was passing of several loose stools, described by the patient as 'diarrhoea'. Clozapine was continued, but 3 days later, the patient's physical health had worsened, with passage of frequent loose stools, a headache, and paraumbilical pain, though denied any nausea, vomiting or chest pain. Temperature peaked at 39.3C and pulse rate 121. However, the patient was eating and drinking adequately and there was no evidence of muscle rigidity. A covid swab was negative and the patient denied any dysuria or frequency. Plan was for stool and urine tests and four times daily monitoring of vital signs. Notably, there was regular daily bowel movements, type 4/5 on the Bristol stool chart (Heaton and Lewis, 1997; Harvey et al., 1992), for at least 5 days in a row prior to the day of clozapine initiation. Thereafter, in the 3 days following clozapine initiation, the patient opened bowels 20 times, averaging 4-5 times of loose watery, non-bloody stools per day. The patient was moved to isolation on suspicion of covid-19 infection or infective gastroenteritis. An ECG showed sinus rhythm, a heart rate of 100 bpm, QTc 405ms and T wave inversion in lead III (noted in previous ECGs). The patient subsequently declined further doses of clozapine, now attributing the physical symptoms to the medication as they were similar to the symptoms on previous trials of clozapine in a different hospital. Temperature and headaches subsided with paracetamol given regularly at 6 hourly intervals.

2.5 With persisting diarrhoea 4th day after initiating clozapine, the team reviewed the possible cause of this presentation. Blood report showed an isolated C-reactive protein (CRP) rise (96mg/L); full blood count (FBC), troponin, creatine kinase (CK), renal and liver function were all normal; only three very small doses of Clozapine had been taken; and crampy abdominal pain was reported on the day following initiation of clozapine. Further investigations showed heavy mixed growth in urine and haematuria; a negative pregnancy test; stool sample was negative for virus. The management plan at this point was to change laxative prescription to 'as required' and commence ondansetron as an antiemetic. The team reviewed this information and concluded that on balance, the clinical picture was more consistent with gastroenteritis than clozapine-induced diarrhoea, but that the latter could not be excluded. The clozapine was discontinued.

2.6 The pyrexia persisted more than 48 hours after the last dose of clozapine; five days after the last dose, stooling had subsided and vital signs were all normal, though the patient still complained of headache. Clinical Knowledge summaries (NICE) guidance advises diarrhoea stool cultures only after four weeks, but the team thought it important from a diagnostic point of view to request a culture earlier and so another stool sample was collected for this purpose; it later returned negative. Two weeks and 3 days after the last dose of clozapine, inflammatory markers had resolved.

2.7 Because the patient's mental state was still very unsettled and there was still uncertainty about the cause of the physical health presentation being due to clozapine, the team decided to discuss administering a small test dose of clozapine, followed a week later by a low dose for a week and then slow escalation if there was no evidence of a further reaction. The patient was adamant about restarting the medication, but the team remained of the view that clozapine was in the patient's best interests and so continued to offer it. Eventually the patient agreed to a one-off trial dose of clozapine 'to be proven right'.

Table 2
Naranjo scale

Question	Yes	No	Do Not Know	Score
1.Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	1
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	1
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	1
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	1
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
	Total Score: 9			

2.8 This time, a stat dose of 12.5mg clozapine was given on day 1 after an FBC report returned normal. The plan was to monitor over the next 12 hours for adverse effects. In the day following, the patient mostly declined physical observations but was observed to be physically well until Day 3, when non-diarrhoeal stools were passed four times through the day. By Day 4, there was a high temperature of 39.6C and tachycardia of 121/min. Other vital signs were normal. The patient reported a headache, cold with shivering, a sore throat and 'bad taste' and was immediately isolated, covid swab and blood taken and infection control protocol followed. No further clozapine had been administered since the one-off dose on day 1. Blood report from day 4 showed CRP 72, repeat 128; FBC was normal except for raised eosinophil count, 0.44 (0-0.4); Troponin was negative; B-type natriuretic peptide (BNP) normal; LFTs normal (Table 1).

2.9 By Day 5 temperature and pulse remained elevated, with the patient reporting groin pain with left upper quadrant tenderness but declined to provide a urine sample. Co-amoxiclav was commenced and paracetamol continued. By day 6, a urine test showed trace nitrites and ketones ++ and a culture later returned negative; pregnancy and covid test were negative and CRP had improved to 93. By day 7 vital signs were all normal and the patient did not report any symptoms. A repeat covid test was negative and inflammatory markers had improved. Though the patient had passed stools between 2-4 times per day since day 3, only one of these was recorded as 'diarrhoeal' stool. Infection prevention Control team (IPC) recommended that the patient remain in isolation area for 14 days even though her COVID-19 Swabs were negative.

2.10 The team finally concluded that with similar episodes of diarrhoea, fever and abdominal pain occurring within 48 hours both times clozapine was initiated on the ward, the balance of probabilities favoured an adverse reaction to clozapine. The conclusion was therefore reached that there would be no further attempts to initiate clozapine.

3. Discussion

3.1 Our case report adds to the relatively few but increasingly reported adverse effect of diarrhoea in relation to clozapine use. The key features of this patient's reaction to clozapine were fever, diarrhoea, abdominal pain and isolated elevated CRP, all of which have been reported in the literature in relation to clozapine use. Peculiar features of the presentation in this case were the rapid onset of diarrhoea and other symptoms on commencement of clozapine, the small dose at which the reaction occurred, and the consistency of the reaction with each trial of clozapine. When these features were subjected to the Naranjo scale (Rask et al., 2020), we got a score of '9', indicating a definite association between clozapine and this reaction (Table 2).

3.2 Existing literature describe diarrhoea as an uncommon side effect of clozapine, (De Fazio et al., 2015, Attard et al., 2019, Linsley and Williams, 2012), unlike constipation which has been reported in 30-60% of patients (De Raad et al., 2011). A recent case report from Finland described this reaction to clozapine in four patients, starting at 1-3 weeks of clozapine treatment and at doses that ranged from 125 to 200mg total daily dose (TDD), leading to discontinuation of clozapine in three of these cases (Linsley and Williams, 2012). In all cases, diarrhoea was accompanied by other features which included fever, nausea and

Table 3
Medications co-prescribed with clozapine.

Medication Regular medications	First trial	Second trial with dose	Third trial with dose
Olanzapine		20mg at night	20mg at night
Valproate		Prescribed as Depakote semisodium valproate 1000mg twice daily, (changed to epilim chrono- sodium valproate MR 2000mg at night to reduce GI side effects)	Prescribed as Epilim chrono- sodium valproate MR 2000mg at night
Haloperidol		10mg at night	10mg at night
Folic acid		5mg once daily	5mg once daily
Clonazepam		0.5mg once daily	0.5mg once daily
Ondansetron		4mg twice daily	4mg twice daily -
Gaviscon		10ml three times daily	-
Colecalciferol		800 units once daily	800 units once daily
Nicotine patch		21mg/24 hours	21mg/24 hours
'As required medications' only			
Clonazepam		0.5-1.0mg, up to 4mg/24 hours (none taken)	0.5-1.0mg, up to 4mg/24 hours
Procyclidine		5mg PO up to 15mg/24h (none taken)	
Paracetamol		1g QDS up to 4g/24h	
Ibuprofen		400mg TDS up to 1.2g/24h (none taken)	
Nicotine lozenge		1mg PRN (none taken)	

vomiting, flu-like symptoms, eosinophilia, and elevated inflammatory markers. The cases in that report shared similar features with an earlier report where three patients developed 'severe' or 'profuse' diarrhoea at 13 days, 6 weeks and 9 months of clozapine treatment respectively, and at clozapine doses of 200mg-450mg daily (Attard et al., 2019). Again, in all 3 cases, clozapine was discontinued and attempts at rechallenge were abandoned when 2 of the patients developed agranulocytosis and neutropenia.

3.3 There have been attempts at explaining diarrhoea associated with clozapine, including that it may be overflow-incontinence from constipation or a result of laxative prescription for constipation (Naranjo et al., 1981); or due to an infective cause sequel to clozapine-induced lymphopenia (Attard et al., 2019), eosinophilic colitis, pseudomembranous colitis, allergies or hypersensitivity reactions, or a DRESS-like phenomenon (Linsley and Williams, 2012, Verdoux et al., 2019). It is also reported that diarrhoea may be a feature of clozapine-induced fever or myocarditis (Attard et al., 2019).

3.4 In the case of this patient, careful consideration was given to exclude potential differentials for the presentation, including repeated covid tests which returned negative; absence of chest pain and a negative troponin test reducing the likelihood of myocarditis; negative stool test for viral colitis; and regular stools prior to, and at initiation of clozapine. Normal amylase result excluded pancreatitis as the cause of the presentation in the first trial, though was not checked in the other 2 trials. We were also able to exclude neuroleptic malignant syndrome (NMS) with normal CK values and an absence of muscle rigidity. Though a blood count showed raised eosinophil during the last clozapine trial, this did not meet NICE-CKS or Karduan et al.'s criteria for a DRESS syndrome. The authors acknowledge that a limitation to this report is that further investigations, including colonoscopy, cardiac MRI, and Echocardiogram might have helped to provide further information on this patient's reaction to clozapine, as would amylase in the second and third trials.

3.5 It is of note that this patient's reaction with diarrhoea to clozapine exposure was with a consistency and increasing severity that would suggest an allergic basis to the reaction. It is therefore important that clinicians be alert to this rare but potential adverse effect of clozapine use.

Criteria for inclusion

authors 1 and 2 were directly involved in the management of the patient, the development of the concept of the paper and writing the article; author 3 was involved in the literature review and discussion for the article; author 4 was involved in sourcing information and in writing the article.

Statement of approval

The authors attest that this manuscript has been read and approved by all the authors and each author believes that the manuscript represents honest work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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