Case Report

HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2022; 9(3):1196-1202

UDC: 615.214.2.065; 616.3

doi:10.5937/hpimj2203196M

Is Clozapine to Blame for Delayed Ogilvie Syndrome and Gastrointestinal Bleeding in Overdose Settings?

Vesna M. Mijatović Jovin[1], Nataša R. Perković Vukčević[2,3], Gordana N. Vuković Ercegović[2,3], Snežana B. Đorđević[2,3], Slavica S. Vučinić[2,3], Zoran P. Šegrt[3], Bela Š. Kolarš[4], Jasmina V. Jović Stošić[2,3],

[1] Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[2] National Poison Control Center, Military Medical Academy, Belgrade, Serbia
[3] Faculty of Medicine of the Military Medical Academy, University of Defense, Belgrade, Serbia
[4] Health Center Novi Sad, Novi Sad, Serbia

SUMMARY

Introduction: Ogilvie syndrome and gastrointestinal bleeding as complications after reversal of typical clinical picture of acute clozapine overdose is described.
Case Report: A previously healthy 31-year-old man was found unconscious with Glasgow Coma Score of 6, non-reactive miotic pupils, hypersalivation and heart rate of 115 bpm. In the blood, the presence of clozapine, diazepam, haloperidol and biperiden were confirmed. The patient was referred to the intensive care unit for symptomatic and supportive treatment. Clinical signs registered on admission, except for sinus tachycardia, were completely resolved by the day 3. The patient began to eat and had regular bowel movements. From the seventh day, gastrointestinal complications were noticed. Nonobstructive dilatation of the stomach and intestine was confirmed on computed tomography scan. Nasogastric suction, the usage of laxatives and prostigmin injections as well as colonic irrigation was performed with a good clinical response.
Conclusion: Clinicians should be aware of the potential of atypical antipsychotics to cause ileus, particulary in combination with other drugs with antimuscarinic properties, and ready to rapidly detect and treat intestinal atony thus preventing life-threatening complications. Serum clozapine levels may not equate to clinical toxicity and the drug-näive patient require more careful observation for complications in clozapine toxicity settings.

Keywords: Atypical Antipsychotics, Clozapine, Acute Overdose, Delayed Complications, Ogilvie Syndrome, Gastrointestinal Bleeding

INTRODUCTION

Clozapine is an atypical antipsychotic with minimal extrapyramidal toxicity, indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard acceptable antipsychotic medication [1]. However, its true potential in treatment-resistant schizophrenia is limited by the complex adverse effects' profile [2].

Corresponding author:
Professor Jasmina V. Jović Stošić, MD, PhD
Specialist in Internal Medicine, Subspecialist in Clinical Toxicology
National Poison Control Center, Military Medical Academy, Crnotravska 17, 11002 Belgrade, Serbia
E-mail: drjasminajovicstosic@gmail.com

© The Serbian Medical Society 2014

Even though gastrointestinal hypomotility was described with typical antipsychotics mainly in association with the use of anticholinergic agents, some of the newer agents, such as clozapine, exhibit intrinsic anticholinergic activity as well [3]. Moreover, a recent study, by using a colonic transit test, provides objective evidence of significant gastrointestinal hypomotility in patients treated with clozapine [4].

Gastrointestinal hypomotility associated with clozapine may cause paralytic ileus, faecal impaction, aspiration of vomit, necrotizing colitis and/or intestinal perforation; fatalities provoked by those (often underrecognized) complications have been reported as well [5]. In addition, acute intestinal pseudo-obstruction (Ogilvie's Syndrome), which is characterized by signs and symptoms of a mechanical obstruction of the small or large bowel in the absence of a mechanical cause, has been related to antipsychotics usage [6-8].

The authors point out that high toxic clozapine concentrations and subsequent paralytic ileus might be infection/inflammation induced in patients on chronic clozapine treatment or due to toxic clozapine ingestion (overdose) [9-15].

A case of a young man who developed gastrointestinal hypomotility and bleeding as complications after reversal of typical clinical picture of acute clozapine overdose is described here.

CASE REPORT

A previously healthy 31-year-old man was found unconscious with Glasgow Coma Score of 6, non-reactive miotic pupils, hypersalivation and heart rate of 115 bpm. Except for sinus tachycardia, the electrocardiogram was read as normal. Laboratory tests on admission were within the reference range except for high serum levels of aspartat-aminotransferase (AST), creatine kinase (CK) and C-reactive protein (CRP) of 149 U/L (reference value <37 U/L), 4171 U/L (reference value <300 U/L) and 210.4 U/L (reference value <5 U/L), respectively. A computed tomography (CT) scan of the brain was negative for acute intracranial disease and lumbar puncture, performed because of an elevated CRP, excluded neuro infection. Abdominal ultrasonography and chest radiography findings were normal. Patient's father afterwards gave information that he had found empty boxes of his own psychiatric medicines (clozapine, haloperidol, biperiden, diazepam). Toxicological screening (HPLC-PDA method) revealed a clozapine level of 0.03 mg/l (therapeutic range: 0.35-0.6 mg/l, toxic concentrations from 0.6-1 mg/l [16]), N-desmethylclozapine level of 2.39 mg/l, diazepam level of 0.17 mg/l (therapeutic range: 0.1-2 mg/l, toxic concentrations from 3-5 mg/l [16]) haloperidol level of 0.04 mg/l (therapeutic range: 0.005-0.017 mg/l, toxic concentrations from 0.05-5 mg/l [16]) and biperiden level of 0.002 mg/l (therapeutic range: 0.05-0.1 mg/l, comatose-fatal concentrations from 0.25 mg/l [16]). The patient was referred to the intensive care unit of toxicology ward for symptomatic and supportive treatment.

On the second day of hospitalization, the patient became febrile (37.8°C). Again, chest X-ray, urinalysis and complete blood analysis, except for CRP, were normal. The patient had persistently elevated heart rate (120-130 bpm), but other clinical signs registered on admission were completely resolved by the day 3. The patient began to eat and had regular bowel movements.

At day 7, the patient complained of abdominal fullness and nausea, followed by vomiting copious quantities of tea-colored fluid. Physical examination showed distended abdomen and decreased bowel sounds. High leucocyte count (10.60×10^9/L– 24.0×10^9/L – 20.0×10^9/L; referent range: 4.0-10.0×10^9/L), with gradually falling levels of hemoglobin (100 – 93 – 80 g/L; referent range: 120-180 g/L) and hematocrit (0.31 – 0.27 – 0.24 L/L; referent range: 0.35-0.54 L/L) were detected. Under the suspicion of gastrointestinal perforation, a plain x ray of the abdomen was indicated. Findings, interpreted by an experienced radiologist, pointed to the existence of subdiaphragmatic free gas or the distended stomach. Nonobstructive dilatation of the stomach, duodenum, jejunum and the proximal parts of ileum was confirmed on CT scan (Figure 1). Esophagogastroduodenoscopy identified distal esophagitis presented with linear ulcerations covered with fibrin; gastric mucosa without changes; both in the esophagus and in the stomach hemorrhagic content; functional nonmechanical gastric outlet obstruction; distended duodenum with numerous shallow ulcerations covered with fibrin, without active bleeding (ischemic changes suspected), abundant blood reflux from distal parts of the

Figure 1. Nonobstructive dilatation of the stomach and intestine confirmed on CT scan.

duodenum. Multislice CT angiography of abdomen excluded occlusion of the mesenteric vessels.

Conservative management with nasogastric suction, the usage of laxatives and prostigmin injections as well as colonic irrigation was performed with a good clinical response. In addition, fluid and electrolytes resustitation including blood products and gastroprotective medications was introduced. During the next several days melena was present.

During hospitalization, the control chest X-ray showed a pneumonic infiltration typical for aspiration bronchopneumonia. Despite the fact that antibiotic treatment had been introduced, the primarily detected process in the lungs was propagated. Because of the acute respiratory failure, the patient required mechanical ventilation for 10 days.

From the day 25, the patient was completely recovered and was discharged from the hospital at day 30.

DISCUSSION

The clinical picture of poisoning in our patient pointed to the dominant effects of clozapine overdose. To the best of our knowledge, gastrointestinal complications of acute clozapine poisoning in the drug-näive patient with the onset in the phase of recovery, after reversal of typical nervous systems disturbances, have not been previously discussed.

In this report, clinical signs of clozapine toxicity (miotic pupils, hypersalivation, high puls rate) were predominated on admission. They were accompanied with high both CRP and serum CK levels. From the second day, benign fever was detected, while from the

seventh day gastrointestinal complications, including esophagitis, paralytic ileus and gastrointestinal bleeding, were noticed.

In comparison to other second-generation antipsychotics, the occurence of gastrointestinal hypomotility as side effect has been most widely reported for clozapine, presumably due to the anticholinergic activity [3, 5]. Moreover, taking into account the antidopaminergic effect of antipsychotics, the underlying mechanism of digestive hypoperfusion and ischemia could be suggested. Due to its DA1 vascular receptors agonistic activity and subsequent vasodilatatory effects at low dose, dopamine could improve the mesenteric perfusion. On the other hand, antipsychotics, as antidopaminergic agents, could play an additional role in digestive ischemia through inhibition of dopamine-dependant mesenteric vasodilatation [17]. The bowel ischemia related to motility disturbances could be also explained by untreated intestinal obstruction or pseudoobstruction, which can provoke not just gastrointestinal bleeding and distension, but also more serious complications such as gastrointestinal necrosis and perforation [18]. The authors agree that fever, abdominal tenderness, rigidity and leukocytosis should raise the posibility of ischemia, toxic megacolon, or perforation [6]. Considering clozapine-induced esophageal complications, Laker et al., in a series of 36 patients treated with clozapine, reported 4 cases who developed upper gastrointestinal symptoms suggestive of reflux oesophagitis within 6 weeks of starting this drug [19].

It is accepted that the acute toxicity of clozapine is much greater in the absence of tolerance to the drug [5, 20]. Hence, Shu-Chin Yu et al., by reporting rapid development of fatal bowel infarction within 1 week after clozapine treatment, raises the issue that the absence of tolerance to clozapine could cause mortality associated with clozapine-induced ischemic bowel at the beginning of the administration [21]. In the review of the French pharmacovigilance datebase, the time between the beginning of antipsychotics involved and onset of the digestive complications was wariable – between 6 days and 20 years, with a median duration of 35 days [22].

Other medication ingested by our patients may also contribute to the emergence of ileus. Even though constipation is a minor side effect of haloperidol therapy, because of its weak anticholinergic effects, significant gastrointestinal hypomotility and rarely paralytic ileus can occure with biperiden [6, 23]. Clinicians should bear in mind that the anticholinergic interaction from the combination of these two drugs with clozapine may be responsible for serious imparment of gastrointestinal hypomotility. In the review by Peyrière et al, 65.8% of patients with antypsychotics-induced digestive complications were treated by at least one concomitant antimuscarinic medication beside clozapine [22].

Clozapine-induced benign fever is also a well-recognized adverse effect, and it is highly advisable for health care professionals to be cognizant of both agranulocytosis and neuroleptic malignant syndrome considering its differential diagnosis [24-26]. Thus, atypical neuroleptic malignant syndrome associated with atypical antipsychotics has been defined as rare small increases in CK, minor muscle rigidity and mild fever [27, 28]. In particular, Levenson's definition of neuroleptic malignant syndrome appears the most flexible because it allows for its diagnosis to be made in the absence of either fever or rigidity [29, 30]. An inflammatory response with an acute phase reaction elevation in CRP and the subsequent fever are caused by the effect of clozapine on the cytokine system via IL-6 and TNF-α as it was postulated by the investigators [31]. Štuhec et al. and Kohen et al., in recently published case reports, discussed development of a benign fever in association with a rise in the CRP level in the patients on clozapine treatment. The fever resolved and CRP level declined progressively with clozapine discontinuation [32, 33].

CONCLUSION

Based on previously presented Clozapine Induced Delayed Ogilvie Syndrome at young 31 year old man, clinicians should be aware of the potential of atypical antipsychotic drugs to cause ileus, particulary in combination with other drugs with antimuscarinic properties, and ready to rapidly detect and treat intestinal atony thus preventing life-threatening complications. In addition, it should be highlighted that serum clozapine levels may not equate to clinical toxicity and the drug-näive patient require more careful observation for complications in clozapine toxicity settings.

ACKNOWLEDGEMENT

The Ministry of Education, Science and Technological Development of the Republic of Serbia (grant numbered 451-03-68/2022-14/200114) and Provincial Secretariat for Higher Education and Scientific Research of the Autonomous Province of Vojvodina (grant numbered 142-451-2331/2022-01) supported this research work.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. Lally J, MacCabe JH. Antiphychotic medication in schizophrenica: a review. Br Med Bull 2015; 114: 169-79.

2. De Fazio P, Gaetano R, Caroleo M, Cerminara G, Maida F, Bruno A, et al. Rare and very rare adverse effects of clozapine. Neuropsychiatr Dis Treat 2015; 11: 1995-2003.

3. De Hert M, Hudyana H, Dockx L, Bernagie C, Sweers K, Tack J, et al. Second-generation antipsychotics and constipation: a review of the literature. Eur Psychiatry 2011; 26: 34-44.

4. Baptista T, Carrizo E, Fernandez E, Connell L, Servigna M, Parra A, et al. Colonic transit diagnostic test shows significant gastrointestinal hypomotility in clozapine-treated patients in comparison with subjects treated with other antipsychotics. Schizophr Res 2015; 166: 207-11.

5. Flanagan RJ, Ball RY. Gastrointestinal hypomotility: an under-recognised life-threatening adverse effect of clozapine. Forensic Sci Int 2011; 206: e31-6.

6. Sheikh RA, Prindiville T, Yasmeen S. Haloperidol and benztropine interaction presentig as acute intestinal pseudo-obstruction. Am J Gastroenterol 2001; 96: 934-5.

7. De Bruin GJ, Bac DJ, van Puijenbroek EP, van der Klooster JM. Ogilvie Syndrome induced by clozapine. Ned Tijdschr Geneeskd 2009; 153: B437.

8. Maloney N & Vargas D. Acute Intestinal Pseudo-Obstruction (Ogilvie's Syndrome). Clin Colon Rectal Surg 2005; 18: 96–101.

9. Kapoor S. Gastrointestinal complications of clozapine therapy secondary to elevated serum levels. Ther Drug Monitor 2013; 35: 144.

10. Leung JG, Nelson S, Takala CR, Goren JL. Infection and inflammation leading to clozapine toxicity and intensive care: a case series. Ann Pharmacother 2014; 48: 801-5.

11. Farha KA, van Vilet A, Knegtering H, Bruggeman R. The value of desmethylclozapine and serum CRP in clozapine toxicity: a case report. Case Rep Psychiatry 2012; 592784.

12. Rondla S & Crane S. A case of clozapine-induced paralytic ileus. Emerg Med J 2007; 24:e12.

13. Sarac H, Henigsberg N, Bagaric-Krakan L. Clozapine-induced paralytic ileus. Psychiatr Danub 2015; 27: 283-4.

14. Cam B & Tanircan MZ. Clozapine-induced paralytic ileus: a case report. Ther Adv Psychopharmacol 2014; 4: 170-2.

15. Nguyen GH, Brahmbhatt N, Heinrich TW. A case report of clozapine-induced severe gastrointestinal hypomotility. Prim Care Companion CNS Disord 2014; 16: 10.4088/PCC.14l01685.

16. Moffat AC, Osselton MD, Widdop B and Watts J. Clarke's Analysis of Drugs and Poisons. 4th edition. London: Pharmaceutical Press; 2011.

17. Hugues AD, Thom SA, Woodall NM, Redman D, Sever PS. Dopamine produces forearm vasodilatation following alpha adrenoceptor blockade by action on vascular dopamine (DA1) receptors in man. J Hypertens 1987; 5: 337–40.

18. Martínez Díaz-Caneja C, González-Molinier M, Conejo Galindo J, Moreno Iñiguez M. Severe bowel ischemia due to clozapine with complete remission after withdrawal . J Clin Psychopharmacol 2010; 30: 463-5.

19. Laker MK & Cookson JC. Reflux oesophagitis and clozapine. Int Clin Psychopharmacol 1997; 12: 37-9.

20. Reith D, Monteleone JP, Whyte IM, Ebelling W, Holford NH, Carter GL, et al. Features and toxicokinetics of clozapine in overdose. Ther Drug Monit 1998; 20: 92-7.

21. Yu SC, Chen HK, Lee SM. Rapid development of fatal bowel infarction within 1 week after clozapine treatment: a case report. Gen Hosp Psychiat 2013; 35: 679. e5 - 679.e6.

22. Peyrière H, Roux C, Ferard C, Deleau N, Kreft-Jais C, Hillaire-Buys D, et al. Antipsychotics-induced ischaemic colitis and gastrointestinal necrosis: a review of the French pharmacovigilance datebase. Pharmacoepidemiol Drug Saf 2009; 18: 948-55.

23. Nielsen J & Meyer JM. Risk factors for ileus in patients with schizophrenia. Schizophr Bull 2012; 38: 592-8.

24. Nittenson NC, Kando JC, Frakenburg FR, Zanarini MC. Fever associated with clozapine administration. Am J Psychiatry 1995; 152: 1102.

25. Tham JC & Dickson RA. Clozapine-induced fevers and 1-year discontinuation rate. J Clin Psychiatry 2002; 63: 880–4.

26. Wang WW, Wang Yu, Xiao P, Zhang P. Neuroleptic malignant syndrome induced by clozapine: a case report and discussion. Klin Psihofarmakol B 2014; 24: 172-5.

27. Karagianis JL, Phillips LC, Hogan KP, LeDrew KK. Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. Ann Pharmacother 1999; 33: 623-30.

28. Trollor JN, Chen X, Chitty K, Sachdev PS. Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. Br J Psychiatry 2012; 201: 52-6.

29. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142: 1137-45.

30. Roge R, Moller BK, Anderson CR, Correll CU, Nielsen J. Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far? Schizophr Res 2012; 140: 204-13.

31. Trollor JN, Chen X, Sanchdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. CNS drugs 2009; 23: 477-92.

32. Kohen I, Afzal N, Hussain S, Manu P. Increases in C-reactive protein may predict recurrence of clozapine-induced fever. Ann Pharmacother 2009; 43: 143–6.

33. Stuhec M. Clozapine-induced elevated C-reactive protein and fever mimic infection. Gen Hosp Psychiatry 2013; 35: 680 e5-6.

Da li je klozapin odgovoran za odloženi Ogilvie sindrom i gastrointestinalno krvarenje u uslovima predoziranja?

Vesna M. Mijatović Jovin[1], Nataša R. Perković Vukčević[2,3], Gordana N. Vuković Ercegović[2,3], Snežana B. Đorđević[2,3], Slavica S. Vučinić[2,3], Zoran P. Šegrt[3], Bela Š. Kolarš[4], Jasmina V. Jović Stošić[2,3]

[1] Katedra za farmakologiju, toksikologiju i kliničku farmakologiju, Medicinski fakultet, Univerzitet u Novom Sadu, Novi Sad, Srbija
[2] Nacionalni centar za kontrolu trovanja, Vojnomedicinska akademija, Beograd, Srbija
[3] Medicinski fakultet Vojnomedicinske akademije, Univerzitet odbrane u Beogradu, Beograd, Srbija
[4] Dom zdravlja Novi Sad, Novi Sad, Srbija

KRATAK SADRŽAJ

Uvod: Opisan je Ogilvie sindrom i gastrointestinalno krvarenje kao komplikacije nakon prestanka tipične kliničke slike akutnog trovanja klozapinom.
Prikaz slučaja: Prethodno zdrav tridesetjednogodišnji muškarac je pronađen bez svesti sa Glasgow Koma Skorom 6, nereaktivnim miotičnim zenicama, hipersalivacijom i srčanom frekvencom od 115 otkucaja/minutu. Potvrđeno je prisustvo klozapina, diazepama, haloperidola i biperidena u uzorku njegove krvi. Pacijent je primljen u jedinicu intenzivne nege radi sprovođena simptomatske i suportivne terapije. Klinički znaci registrovani na prijemu, osim sinusne tahikardije, u potpunosti su prestali do 3. dana. Pacijent je počeo da jede i imao je urednu peristaltiku creva. Komplikacije od strane gastrointestinalnog trakta su registrovane od 7. dana. Neopstruktivna dilatacija želuca i creva je potvrđena kompjuterizovanom tomografijom. Primenjeni su nazogastrična sukcija, laksativi, injekcije prostigmina kao i irigacija kolona, sa dobrim kliničkim odgovorom.
Zaključak: Kliničari treba da budu svesni da atipični antipsihotici imaju potencijal da prouzrokuju ileus, posebno u kombinaciji sa drugim antimuskarinskim lekovima, i spemni da brzo prepoznaju i leče atoniju creva tako prevenirajući životnougrožavajuće komplikacije. Koncentracija klozapina u serumu ne mora korelirati sa kliničkom slikom i pacijenti koji nisu imali ranija iskustva sa lekom zahtevaju pažljiviju observaciju u sličaju trovanja klozapinom.

Ključne reči: atipični antipsihotici, klozapin, akutno trovanje, odložene komplikacije, Ogilvie sindrom, gastrointestinlo krvarenje

Received: June 08, 2022
Accepted: July 29, 2022