Case Report

Clozapine-induced intestinal occlusion: a serious side effect

Lorenzo Pelizza, Pasquale De Luca, Maurizio La Pesa, Daniela Borella

Casalmaggiore Psychiatric Operative Unit n. 25 - "Oglio Po" General Hospital, Cremona Hospital Institutes, Italy

Abstract. Aim of this article is to describe the first italian case reported in literature of a clozapine-induced intestinal occlusion with previous severe constipation in a 45-year-old male patient who had been treated with daily clozapine for 5 months because of treatment-resistant residual schizophrenia. When conservative treatment (intravenous fluids, fleet enema and rectal washout) was used and clozapine therapy was decreased, gastrointestinal symptoms rapidly improved and the patient had regular bowel motions within a week. Preventive measures (high-fiber diet, adequate fluid intake, stool softeners and exercise) was also used to ensure that clozapine therapy could be safely continued. Although constipation is a common and usually benign side effect of treatment with clozapine, this case-report highlights the consequences of undertreated and unrecognized marked constipation progressing to severe bowel obstruction (a complication which deserves more attention because it can lead to hospitalization and might be potentially fatal). (www.actabiomedica.it)

Key words: Clozapine, constipation, intestinal occlusion, schizophrenia

Introduction

Clozapine is an atypical antipsychotic drug commonly used in the therapy of patients with treatment-resistant schizophrenia (1-3). Despite its demonstrated efficacy in psychotic disorders (it can result in dramatic improvements in many refractory schizophrenics, where it has been found to be superior to traditional neuroleptics) (4-6), the widespread use of clozapine has been limited by its potential adverse effects (such as life-threatening agranulocytosis, seizures, hypotension, weight gain, sialorrhea) (7-10).

Constipation is a common, albeit less known, side effect of clozapine which occurs in 14-60% of treated patients (11-16). It is attributed to the combination of poor bowel habits (low-fiber diet, inadequate fluid intake, diminished exercise) (17) and clozapine's strong anticholinergic properties (18, 19). In this way, clozapine appears to be the most antimuscarinic of the antipsychotic medications (it is an antagonist at M_3 and M_5 receptors and a partial agonist of M_1 and M_2 receptors) (20, 21). Its anticholinergic properties are comparable in strength to those of amitriptyline and benztropine, which have the most potent antimuscarinic effects among the psychotropic drugs (22, 23). Other associated medications with antimuscarinic activity (such as traditional neuroleptics, tricyclic antidepressants and antiparkinson drugs) may also increase clozapine's anticholinergic burden and exacerbate constipation (1, 10, 17).

Clozapine-induced constipation is one such side effect which must be taken seriously (24). In fact, it may result in intestinal occlusion, paralytic ileus and death (11, 25-27). A recent edition of the Australian Adverse Drug Reactions Bulletin (18) highlighted the common (but not trivial) nature of constipation. Of the 15 cases of this serious side effect reported in Australia between 1992 and 1999, nine involved fecal impaction, two involved sub-acute bowel obstruction and there was one fatality (24) secondary to inhalation of feculent vomiting after occlusion of the transverse colon. This fatal case is remarkably similar to the five previously published cases reviewed by Levin et al (25). Clinically, there seem to be two mechanisms whereby clozapine-induced constipation can have a fatal outcome. In three cases (28-30), intestinal ob-

struction led to distention and necrosis of the bowel and presented as an acute abdomen with a picture of feculent peritonitis and sepsis. In the remaining two cases (11, 26), postmortem examinations revealed severe pulmonary edema secondary to inhalation of feculent vomiting due to an extensive fecal impaction involving the entire large bowel.

Herein, we describe the first italian case reported in literature of clozapine-induced intestinal occlusion with previous severe constipation to highlight how it is important for prescribers to recognise and treat (as soon as possible) constipation in patients taking clozapine in order to prevent the development of more serious complications.

Case report

A 45-year-old male patient with a 27-year history of treatment-resistant residual schizophrenia (with much institutional care) and excellent past physical health (he had no prior history of constipation or other gastrointestinal symptoms or diseases) had been treated with clozapine (400 mg/die) for the past 5 months before his admission in our hospital, obtaining a significant psychopathological benefit. At the time of hospitalization, he resided in a community mental health facility and was also receiving lorazepam (2.5 mg/die) for a recurrent starting insomnia and sertraline (100 mg/die) as augmentation for his antipsychotic (negative symptoms) medication. His plasma clozapine levels were within therapeutic limits (490 ng/mL for clozapine and 280 ng/mL for norclozapine) (31, 32).

On admission, the patient reported a three-week history of severe constipation and subjective abdominal distention (without pain), followed by two episodes of biliary vomiting on the same day. In the week before his hospitalization, he also complained of intermittent fever (temperature > 38° C) and coughing fits probably due to his marked sialorrhea (chest X-ray appearance, in fact, was normal and ECG showed no pathological findings). Physical examination revealed diffuse abdominal tenderness which was soon accompanied by marked abdominal distention (without pain), colon cord sensation in the right iliac fossa and decreased bowel sounds. Rectal examination also revealed the existence of a fecaloma. A slight leukocytosis (10760 white cells per mL [87% neutrophils, 9% lymphocytes, 2% monocytes and 2% eosinophils) with a neutrophilia of 8100 cells per mL and a lymphopenia of 700 cells per mL were the only abnormal laboratory findings (creatinine, urea and electrolytes, in fact, were normal and liver function values were within the normal range). Abdominal X-ray appearance showed dilated loops of the small and large bowel (with no evidence of air-fluid levels) and a loaded colon (megacolon) with extensive severe fecal impaction mainly involving its transverse and descending portions. A contrast enema also revealed no gross structural lesions. Based on those findings, a diagnosis of intestinal occlusion was made.

Over the following week, the ileus resolved with conservative treatment (intravenous fluids, fleet enema and rectal washout), while clozapine therapy had been decreased to a dose of 250 mg/die. After the intestinal obstruction had resolved, the patient fully recovered within four days of treatment, had regular bowel motions within a week and preventive measures (high-fiber diet, adequate fluid intake, stool softeners and exercise) were used to ensure that clozapine therapy could be safely continued.

Discussion

Although constipation is a common and usually benign side effect of treatment with clozapine (it occurs in 14-60% of treated schizophrenics) (10-16), this case-report highlights the consequences of undertreated and unrecognized marked clozapine-associated constipation progressing to severe bowel obstruction. This is perhaps the overriding and important message of this article: clozapine-induced constipation and its clinical complications are not rare and they deserve more attention since they can lead to hospitalization and death (24, 27). Schizophrenic patients on clozapine should be warned of these problems and be asked (regularly) concerning their bowel function. Due to the increasing number of psychiatric subjects taking clozapine that are treated in the community, psychiatrists as well as other specialists and general practitioners ought to be aware of clozapine-

associated constipation and its complications (particularly, of the possible development of an intestinal occlusion). With regard to this severe consequence, eight cases (0.13%) of paralytic ileus were found in 8000 Chinese psychiatric patients (33) and two cases (0.25%) of bowel sub-occlusion were found in 929 German schizophrenics (7). Three cases of intestinal occlusion (10%), one of them fatal, were also reported among 30 clozapine-treated psychotic subjects in a French hospital (26). According to Hayes and Gibler (11), most constipated patients on clozapine were mild to moderate in severity and adequately responded to stool softeners or bulk-forming laxatives, while only 12% required repeated use of enemas to relieve severe constipation.

Another common element to highlight is that the diagnosis of constipation and its complications was often difficult or delayed in schizophrenic subjects treated with clozapine (25). Their gastrointestinal symptoms were either nonspecific (i.e. "false diarrhea" of constipated patients) or not appreciated as heralding a possibly fatal condition. There may be a number of reasons for this, which are briefly considered below. Schizophrenics can have altered sensitivity to pain (34-36) (this phenomenon may be particularly important in the diagnosis of the acute abdomen, because pain is usually the central feature). The precise degree of pain insensitivity is unclear. Neuroleptic medications can have sedative or pain-modulating effects and this may be a confounding factor in medicated patients. It is noteworthy, however, that the syndrome of pain insensitivity was well described before antipsychotic drugs were introduced (37). Another possibility is that pain perception is normal but that schizophrenic subjects show difficulty in expressing the pain that they feel (36). For example, the negative symptoms of schizophrenia may affect the expression of pain and physicians may be misled by flattened affect and apathy into minimizing pain symptoms. Moreover, psychotic patients with a formal thought disorder can have difficulty in organizing their thoughts to express symptoms of pain. Paranoia (i.e. persecutory or hypochondriac delusions) may also discourage physicians from thoroughly evaluating their patients. Furthermore, in the face of a florid psychotic illness, constipation may be trivialized as a minor side effect, acceptable in light of the difficulty of managing an acute psychosis. Moreover, the nature of the schizophrenic disorder requires a team management approach. Consequently, the patient can first report constipation to a mental health worker who may not appreciate its implications. The psychiatrist is often the next in line to hear about the symptoms. The general physician and gastroenterologist, who have the expertise to deal with the diagnosis and management of constipation, may be involved only relatively late.

Future attention should focus on both the pathophysiology and management of constipation and its complications. The pathophysiology of clozapine-induced constipation and intestinal occlusion have always been assumed to be due to an anticholinergic side effect of the medication (an atropinic reaction causing a diffuse bowel hypomotility and the possible formation of fecalomas), but this has never been rigorously investigated or systematically tested in a controlled manner (25). Diagnostic and treatment protocols for clozapine-induced constipation, therefore, must be developed and tested for both inpatient and outpatient settings (11).

Since bowel obstruction seems to be preceded by a (more or less) long time of constipation, standard measures to prevent fecal impaction are strongly recommended (10, 27). In addition, since the prevalence and severity of constipation seem to be dose-dependent (38), a logical strategy is to minimize the dose of clozapine (25). Measurement of serum clozapine levels may be helpful in this regard. If serum levels of clozapine are in the range of 500-700 ng/mL or greater, then the dose can be cautiously lowered (serum levels lower than 350 ng/mL are associated with a lack of clinical response) (31). Another strategy suggested by Levin et al (25) is to replace part of the clozapine dose with a less antimuscarinic antipsychotic drug (such as quetiapine or haloperidol) and thus use it as a clozapine-sparing agent (this strategy of combination therapy has demonstrated to improve glycemic control and reduce weight gain in schizophrenic patients previously treated with clozapine alone) (39). Moreover, Hayes and Gibler (11) have recommended a slower clozapine titration schedule with small increments in the dose of medication by no more than 25 mg/die to a maximum of 100 mg/week.

Conclusion

In conclusion, psychiatrists, general physicians and radiologists should be aware of the seriousness of clozapine-induced constipation and of the risk of progression to bowel occlusion (particularly, in those schizophrenics with a long history of high-dose antipsychotic treatment before clozapine therapy [which may have contributed to less bowel motility] and in those psychotic subjects with prolonged inpatient hospitalization [who are less likely to be active]). Psychiatrists should actively question about symptoms of constipation in this group of patients and have a lowered threshold for investigation and treatment (a patient receiving clozapine and presenting with abdominal pain or vomiting against a background of constipation should raise immediate concern). Prophylactic treatment and prompt intervention for constipation along with slower clozapine titration appear to have been successfull in decreasing the prevalence and severity of clozapine-induced constipation in this psychiatric population, where this adverse drug reaction may lead to bowel occlusion (needing of an hospitalization) and can be potentially fatal (as well as agranulocytosis) (40).

References

1. American Psychiatric Association (APA). Treatment recommendations for patients with schizophrenia. Washington DC, APA Press, 2004.
2. Stahl S. Essential psychopharmacology. Cambridge, Cambridge University Press, 1998.
3. Hardman J, Limbird L, Molinoff P. Goodman & Gilman's pharmacological basis of therapeutics. New York, McGraw-Hill, 1996.
4. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for treatment-resistant schizophrenia: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45: 789-96.
5. Baldessarini R, Frankenburg F. Clozapine: a novel antipsychotic agent. *New Eng J Med* 1991; 324: 746-54.
6. Meltzer H. Treatment of schizophrenia. Washington DC, APA Press, 1995.
7. Grohmann R, Ruther E, Sassim N, Schmidt L. Adverse effects of clozapine. *Psychopharmacol* 1989; 99: 101-4.
8. Safferman A, Lieberman J, Kane J, Szymanski S, Kinon B. Update on the clinical efficacy and side effects of clozapine. *Schizophr Bull* 1991; 17: 247-61.
9. Marinkovic D, Timtijevic I, Babinsky T, Totic S. The side effects of clozapine: a four year follow-up study. *Prog Neuropsychopharmacol* 1994; 18: 537-44.
10. Young C, Bowers M, Mazure C. Management of the adverse effects of clozapine. *Schizophr Bull* 1998; 24: 381-90.
11. Hayes G, Gibler B. Clozapine-induced constipation. *Am J Psychiatry* 1995; 152: 2.
12. Claghorn J, Honigfeld G, Abuzzahab F. The risks and benefits of clozapine versus chlorpromazine. *J Clin Psychopharmacol* 1987; 7: 337-84.
13. Fitton A, Heel R. Clozapine: a review of its pharmacological properties and therapeutic use in schizophrenia. *Drugs* 1990; 5: 722-747.
14. Potter W, Ko G, Liang D. Clozapine in China: a review and preview of US/PRC collaboration. *Psychopharmacol* 1989; 99: 87-91.
15. Singer K, Lam C. Evaluation of clozapine in schizophrenia with acute symptomatology. *J Int Med Res* 1973; 1: 622-9.
16. Lieberman M, Safferman A, Pollack S. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *Am J Psychiatry* 1994; 151: 1744-52.
17. Mathew T, Desmond P, Isaacs D. Constipation: it can be severe with clozapine. *Aust Adverse Drug Reactions Bull* 1999; 18: 2.
18. Jann M, Grimsley S, Gray E, Chang W. Pharmacodynamics and pharmacokinetics of clozapine. *Clin Pharmacokinet* 1993; 24: 161-76.
19. Chengappa K, Pollock B, Parepally H, Levine J. Anticholinergic differences among patients receiving standard clinical doses of olanzapine and clozapine. *J Clin Psychopharmacol* 2000; 20: 311-6.
20. De Leon J, White A, Josiassen R, Diaz F, Simpson G. Serum antimuscarinic activity during clozapine treatment. *J Clin Psychopharmacol* 2003; 23: 336-41.
21. Ichikawa J, Dai J, O'Laughlin I. Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens and striatum. *Neuropsychopharmacol* 2002; 26: 325-39.
22. Bloom F, Kupfer D. Psychopharmacology, the fourth generation in progress. New York, Raven Press, 1994.
23. De Leon J, Canuso C, White A. A pilot effort to determine benztropine equivalents of anticholinergic medications. *Hosp Comm Psychiatry* 1994; 45: 606-7.
24. Drew L, Herdson P. Clozapine and constipation: a serious issue. *Aust NZ J Psychiatry* 1997; 31: 149-50.
25. Levin T, Barrett J, Mendelowitz A. Death from clozapine-induced constipation. *Psychosomatics* 2002; 43: 71-3.
26. Theret L, Germaine M, Burde A. Current aspects of the use of clozapine in the Chalons-sur-Marne Psychiatric Hospital: intestinal occlusion with clozapine. *Ann Med Psychol (Paris)* 1995; 153: 474-7.
27. Tang W, Ungvari G. Clozapine-induced intestinal obstruction. *Aust NZ J Psychiatry* 1999; 29: 660.
28. Shammi C, Remington G. Clozapine-induced necrotizing colitis. *J Clin Psychopharmacol* 1997; 17: 230-2.
29. Commitee on Safety of Medicines/Control Agency. Cloza-

pine and gastrointestinal obstruction. *Curr Prob Pharmacovigilance* 1999; 25: 1.
30. Freudenreich O, Goff D. Colon perforation and peritonitis associated with clozapine. *J Clin Psychiatry* 2000; 61: 950-1.
31. Perry P, Miller D, Arndt S, Cadoret R. Clozapine and norclozapine plasma concentrations and clinical responses of treatment-refractory schizophrenic patients. *Am J Psychiatry* 1991; 148: 231-5.
32. Kronig M, Munne R, Szymanski S, Safferman A. Plasma clozapine levels and therapeutic response for treatment-refractory schizophrenic patients. *Am J Psychiatry* 1995; 152: 179-82.
33. Lu M. Clinical analysis of the main side effects of clozapine. *Chinese J Neurol Psychiatry* 1991; 24: 71-4.
34. Dworkin R. Pain insensitivity in schizophrenia: a neglected phenomenon and some implications. *Schizophr Bull* 1994; 20: 235-48.
35. Rosenthal S, Porter K, Coffey B. Pain insensitivity in schizophrenia: case-report and review of the literature. *Gen Hosp Psychiatry* 1990; 12: 319-22.
36. Bickerstaff L, Harris S, Leggett R. Pain insensitivity in schizophrenic patients: a surgical dilemma. *Arch Surg* 1988; 123: 49-51.
37. Bender L, Schilder P. Unconditioned and conditioned reactions to pain in schizophrenia. *Am J Psychiatry* 1930; 3: 365-84.
38. Pare J, Riffand P, Baurdeix I. The clozapine in France. *Information Psychiatric* 1993; 4: 389-97.
39. Reinstein M, Sirotovskaya L, Jones L. Effect of clozapine-quetiapine combination therapy on weight and glycemic control. *Clin Drug Invest* 1999; 18: 99-104.
40. Klimke A, Kleiser E. Side effects and efficacy of clozapine in the treatment of acute schizophrenia. *Pharmacopsychiatr* 1992; 25: 107.

Accepted: 24th April 2007
Correspondence: Pelizza Lorenzo, MD
c/o Centro Salute Mentale Guastalla
Via Salvo D'Acquisto n. 7
42016 Guastalla (RE)
Tel. 0522/837561
Fax number: 0522/838980
E-mail: anolino@yahoo.it, www.actabiomedica.it