

# DRUG BULLETIN

Pharmacy Department 56 Mooro Drive Mount Claremont WA 6010  
Telephone (08) 9347 6681 Email GHParmacy@health.wa.gov.au Fax (08) 9384 4586

## Clozapine and Gastrointestinal Adverse Effects – A Pain in the Gut?

Graylands Hospital Drug Bulletin 2004 Vol. 12 No. 3 September ISSN 1323-1251

Gastrointestinal adverse effects of clozapine are very common and include nausea, vomiting and constipation. Other troublesome unwanted effects include dry mouth and hypersalivation, which involve the autonomic nervous system.

Constipation is a particularly common adverse effect that has been reported to occur in 14-60% of patients<sup>1,2</sup>. The management of clozapine-induced constipation has been the subject of a past Drug Bulletin<sup>3</sup>. Clozapine's association with constipation could be explained by its potent anticholinergic properties.

Rarely, clozapine-induced constipation has led to serious complications including ileus, bowel obstruction and necrotising colitis. A review was conducted to determine what serious gastrointestinal adverse effects have been reported in the literature and these are discussed below.

### Faecal Impaction

There are three reported cases of death secondary to clozapine-induced constipation and faecal impaction<sup>2,4,5</sup>.

One case involved a 49 year old man who had been receiving clozapine for two years, who died of severe pulmonary oedema secondary to inhalation of feculent vomitus<sup>4</sup>. Another case in a 43 year old man who had been treated with clozapine for six years, suffered a large-bowel obstruction secondary to faecal

impaction<sup>5</sup>. The patient died three weeks after presentation from refractory shock and progressive multi-system organ failure, despite maximal care.

A further case involved a 29 year old man who had only been taking clozapine for 36 days<sup>2</sup>. He died after aspiration of vomitus secondary to bowel obstruction.

### Intestinal Obstruction/Occlusion

There is a French report of three cases of intestinal occlusion in clozapine treated patients, one of which was fatal<sup>6</sup>.

Another report describes two cases of clozapine-induced intestinal obstruction<sup>7</sup>. One of these involved a 51 year old man with no past history of constipation, who had been taking clozapine for two months. He suffered from an intestinal obstruction, from which he fully recovered and clozapine was recommenced. The other case involved a 35 year old woman who had been taking clozapine for four months when she developed abdominal symptoms. She was diagnosed with intestinal obstruction which resolved with treatment and clozapine was continued.

An analysis of side effects in 7921 clozapine patients in China found the main overall side effects occurred in 600 patients. There were 8 patients from this 600 patient sample who had paralytic intestinal obstruction<sup>8</sup>.

### **Paralytic Ileus**

There has been a case reported of post-operative paralytic ileus in a 42 year old man who had been taking clozapine for over a year<sup>9</sup>. Throughout the 14 months of follow-up after surgery, the patient experienced no subsequent gastrointestinal tract symptoms.

### **Colon Perforation and Peritonitis**

A case of a perforated colon and peritonitis has been reported in a 49 year old man who had been treated with clozapine for six weeks<sup>10</sup>. However, the patient had a long history of constipation prior to clozapine. He survived after a hemicolectomy and colostomy, though did suffer a massive cerebrovascular accident peri-operatively, resulting in dense hemiplegia.

### **Gastric Outlet Obstruction**

There has been a reported case of possible clozapine-induced gastric outlet obstruction in a 35 year old man treated with clozapine<sup>11</sup>. The patient recovered once clozapine was ceased and the authors suggest gastrointestinal medications should be instituted with caution in clozapine patients so as not to mask serious adverse effects.

### **Necrotising/Ischaemic Colitis**

A case involving a 36 year old man who developed necrotising colitis is reported<sup>12</sup>. The patient had a history of upper gastrointestinal complaints and constipation prior to clozapine use and had been treated with clozapine for 4 months. Unfortunately the case had a fatal outcome, which the pathology report speculated was secondary to the anticholinergic effects of clozapine and/or benzotropine.

### **ADRAC Reports**

ADRAC (Adverse Drug Reactions Advisory Committee) has received the following reports associated with clozapine treatment in Australia:

- 5 reports of colitis
- 2 reports of ileus
- 3 reports of paralytic ileus

- 14 reports of intestinal obstruction
- 1 report of intestinal perforation
- 1 report of peritonitis
- 2 reports of small intestinal obstruction,

Some of these cases were fatal, but as some of the reports may have overlapped, it is unclear how many deaths there were in total.

Nonetheless, of the 43 constipation-related reports ADRAC has received in total, it appears that 5 cases have been fatal.

It would also appear that the drug companies who supply clozapine in Australia and overseas may have further unpublished reports of serious gastrointestinal adverse effects. In Australia, drug companies should report these cases to ADRAC.

### **Other Antipsychotics**

Constipation is a common side effect of the highly anticholinergic antipsychotic drugs. By promoting intestinal stasis, antipsychotic drugs “may very rarely cause increased intra-abdominal pressure and disrupt the vascular supply to the gut, leading to necrotising enterocolitis”<sup>13</sup>.

One author found approximately 20 cases of necrotising colitis linked to other neuroleptics reported in the literature<sup>12</sup>.

Phenothiazine antipsychotics were most often implicated, especially when used in conjunction with tricyclic antidepressants and anticholinergics.

A further literature search recovered more cases of necrotising colitis, ischaemic colitis or paralytic ileus associated with other psychotropic medications<sup>14-21</sup>.

There are cases of the phenothiazine medication cyamemazine (available in France and Portugal) and chlorpromazine, being associated with acute necrotising colitis<sup>14,15</sup>. Ischaemic colitis has been associated with chlorpromazine, pericyazine, clopenthixol, imipramine and amitriptyline<sup>16,17,18</sup>. Paralytic ileus has been seen in patients treated with chlorpromazine, trifluoperazine and haloperidol<sup>19,20</sup>.

In many of the cases, more than one anticholinergic psychotropic medication was prescribed concurrently.

### Prevention

Monitoring patients for constipation is often difficult but important. Considering the potential for serious and life threatening complications from constipation, it is advisable for all prescribers of psychotropic medications to ensure that bowel habits are monitored and prophylaxis against constipation provided<sup>3</sup>.

For further information on management of clozapine-induced constipation, please refer to the past Drug Bulletin article<sup>3</sup>.

One hospital in the United States, that found a prevalence of constipation in 60% of their clozapine-treated patients, formulated a clozapine constipation protocol<sup>2</sup>. This protocol was instituted along with prompt intervention for constipated patients and a slower titration of clozapine doses.

A fairly common element of the cases reported in the literature is that diagnosis was often difficult or delayed. One author suggests that it is important to have a low threshold for further investigation of potentially serious medical conditions in patients with chronic mental illness<sup>10</sup>. This is particularly important as patients are often less able to clearly describe their symptoms and patients with schizophrenia may have an increased pain threshold<sup>10</sup>.

**A summary of the common recommendations would suggest that standard measures to prevent constipation are important, increases in clozapine dosage should be made in small increments, other anticholinergic medication should be instituted with care and prompt recognition and intervention for constipation is necessary<sup>2,5,7,10</sup>.**

**A patient receiving clozapine, with a background of constipation and presenting with abdominal pain, should be a cause for immediate concern.**

### References:

1. Young CR, Bowers MB, Mazure CM. Management of the adverse effects of clozapine. *Schizophrenia Bulletin* 1998; 24(3): 381-390.
2. Hayes G, Gibler B. Clozapine-induced constipation. *Am J Psychiatry* 1995; 152(2): 298.
3. Management of clozapine-induced constipation. *Graylands Hospital Drug Bulletin* 1998; 7(1).
4. Drew L, Herdson P. Clozapine and constipation: a serious issue. *Aust NZ J Psychiatry* 1997; 31(1): 149-150.
5. Levin TT, Barrett J, Mendelowitz A. Death from clozapine-induced constipation: case report and literature review. *Psychosomatics* 2002; 43(1): 71-73.
6. Theret I, Germain ML, Burde A. [Current aspects of the use of clozapine in the Chalons-sur-Marne psychiatric hospital: intestinal occlusion with clozapine]. [French]. *Annales Medico-Psychologiques* 1995; 153(7): 474-477.
7. Tang WK, Ungvari GS. Clozapine-induced intestinal obstruction. *Aust NZ J Med* 1999; 29(4): 560.
8. Lu MK. Clinical analysis in the main side effects of clozapine: enclosed 600 cases report]. [Chinese]. [*Chinese Journal of Neurology and Psychiatry*] 1991; 24(92): 71-74.
9. Erickson B, Morris DM. Clozapine-associated postoperative ileus: case report and review of the literature. *Arch Gen Psychiatry* 1995; 52(6): 508-509.
10. Freudenreich O, Goff DC. Colon perforation and peritonitis associated with clozapine. *J Clin Psychiatry* 2000; 61(12): 950-951.
11. Schwartz BJ, Frisolone JA. A case report of clozapine-induced gastric outlet obstruction. *Am J Psychiatry* 1993; 150(10): 1563.
12. Shammie CM, Remington G. Clozapine-induced necrotizing colitis. *J Clin Psychopharmacol* 1997; 17(3): 230-231.
13. Simpson GM, Pi EH, Sramek JJ. Neuroleptic and antipsychotic drugs. In: Dukes MNG, Aronson JK, editors. *Meyler's side effects of drugs*. 14<sup>th</sup> ed. Amsterdam: Elsevier Science B.V.; 2000. p.139-163.
14. Ausser A, Leroy C, Bazin B, Sarraz-Bournet B, Oureib J, Georges H. [Acute necrotizing enterocolitis during a prolonged treatment with neuroleptic]. [French]. *Presse Medicale* 1995; 24(12): 577-579.
15. Hay AM. Association between chlorpromazine therapy and necrotizing colitis: report of a case. *Dis Colon Rectum* 1978; 21(5): 380-382.
16. deSilva P, Deb S, Drummond Rd, Rankin R. A fatal case of ischaemic colitis following long-term use of neuroleptic medication. *J Intellect Disabil Res* 1992; 36(4): 371-375.
17. Patel Yj, Scherl ND, Elias S, Chessler RK, Zingler BM. Ischaemic colitis associated with psychotropic drugs. *Dig Dis Sci* 1992; 37(7): 1148-1149.
18. Gollock JM, Thomson JP. Ischaemic colitis associated with psychotropic drugs. *Postgraduate Medical Journal* 1984; 60(706): 564-565.
19. Giordano J, Canter JW, Huang A. Fatal paralytic ileus complicating phenothiazine therapy. *Southern Medical Journal* 1975; 68(3): 351-353.
20. Gaszner G, Kosza P. [Paralytic ileus during haloperidol therapy] [abstract]. [Hungarian]. *Neuropsychopharmacologica Hungarica* 2004; 6(1): 36-38.
21. Feneyrou B, Alauzen M, Bourguin N, Carabalona P. [Necrotizing colitis caused by neuroleptics]. [French]. *Gastroenterol Clin Biol* 1985; 9(8-9): 635-636.

#### Acknowledgment

This article was prepared by Anouska Feszczur and reviewed by the Pharmacy Department.

Comments are welcome at the e-mail address:

[DrugInformation.Graylands@health.wa.gov.au](mailto:DrugInformation.Graylands@health.wa.gov.au)

# The Effects of Smoking and Caffeine on Atypical Antipsychotics

## Smoking

Patients with a mental illness are two to three times more likely to smoke cigarettes than the general population<sup>1</sup>.

By-products of tobacco smoking are metabolic inducers of the cytochrome P450 isoenzyme 1A2 (CYP1A2) and of the less understood UDP-glucuronosyltransferases (UGTs)<sup>2</sup>. These metabolic-inducing by-products can also be expected to be contained in marijuana smoke.

Inducing metabolism requires the synthesis of new enzymes, so it is normally a few weeks after treatment with an inducer has been commenced, that maximum effects are seen. Once an inducer is stopped, it may be a few weeks before the effects disappear.

## Caffeine

Caffeine is more than 90% dependent on CYP1A2 for its metabolism. It may competitively inhibit the metabolism of other medications that are also metabolised by CYP1A2<sup>2</sup>.

Caffeine's metabolism is induced in patients who are smokers, so smokers need three to four times the same amount of caffeine as non-smokers to get the same plasma caffeine levels<sup>2</sup>.

## Effects on Atypical Antipsychotics

There is only a limited amount of literature published regarding smoking and caffeine effects on atypical antipsychotics. However, it would appear that atypical antipsychotics that are not dependant on CYP1A2 or UGT for their metabolism, should not have their levels affected by smoking or caffeine<sup>2</sup>.

Therefore, quetiapine (mainly metabolised by CYP3A), amisulpride (only minimal metabolism), risperidone and aripiprazole (both metabolised by CYP2D6 and CYP3A) should not be affected<sup>2,3</sup>.

Both clozapine and olanzapine's metabolism are mainly dependent on CYP1A2 or UGTs, therefore smoking or caffeine may affect their levels.

## Clozapine

Smoking decreases the average patient's clozapine plasma levels by a correction factor of

1.5<sup>2</sup>. Therefore, if a smoking patient stabilised on clozapine were to stop smoking, their level would likely increase by 1.5, two to four weeks later.

Caffeine increases clozapine levels and an average correction factor is 0.6<sup>2</sup>. Only high amounts of caffeine seem to have a significant interaction with clozapine, however no published data is available to define what quantity of caffeine is "safe" for patients taking clozapine.

## Olanzapine

Studies have shown smoking decreases olanzapine levels<sup>2</sup>. There are no studies looking at caffeine's effects on olanzapine levels, however the pharmacological information would suggest olanzapine levels would be increased.

As olanzapine's therapeutic window is not as narrow as clozapine, these effects on olanzapine levels may not be as clinically relevant.

## Other Medications That May Be Affected

Medications that are mainly dependant on CYP1A2 or UGTs for their metabolism would be expected to have their levels affected by smoking and possibly consuming high amounts of caffeine.

Psychotropic medications that may be affected include haloperidol, chlorpromazine, fluvoxamine, mirtazapine, amitriptyline, clomipramine, imipramine and propranolol.

## Conclusions

Clinicians should be aware that variations in a patient's smoking or caffeine consumption may cause changes in the plasma levels of their medications. Regular monitoring where appropriate would be advised.

### References:

1. Ziedonis DM, Williams JM. Management of smoking in people with psychiatric disorders. *Curr Opin Psychiatry* 2003;16:305-315.
2. de Leon J. Atypical antipsychotic dosing; the effect of smoking and caffeine. *Psychiatric Services* 2004; 55(5): 491-493.
3. Curran MP, Perry CM. Amisulpride. *Drugs* 2001; 61(14): 2123-2150.

### Acknowledgment

This article was prepared by Anouska Feszczur and reviewed by the Pharmacy Department.

Comments are welcome at the e-mail address:

*DrugInformation.Graylands@health.wa.gov.au*