

# Clozapine and constipation

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually.

This information is provided for healthcare professionals and should not be used as a patient information leaflet.

## Background

The Summary of Product Characteristics (SPC) for Clozaril<sup>®</sup> (clozapine) lists constipation as a very common (>1/10) reaction to Clozaril<sup>®</sup>. Intestinal obstruction, paralytic ileus and faecal impaction are listed as very rare (<1/10,000).<sup>1,2</sup>

*The SPC continues:*

Probably on account of its anticholinergic properties, Clozaril<sup>®</sup> has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus. On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.

Paralytic ileus is a contraindication to Clozaril<sup>®</sup> use.

## Incidence and mechanism

Constipation is a very common side-effect of clozapine with a reported incidence in the literature of up to 60%.<sup>3,4</sup> Shirazi *et al* (2016), in a systematic review and meta-analysis of 32 studies, identified a prevalence of 31.2% with patients on clozapine significantly more likely to be constipated than those on other antipsychotics.<sup>5</sup>

Constipation with clozapine is probably due to its anticholinergic properties<sup>1,2</sup> but antagonism of serotonergic and histamine H1 receptors may contribute to the effect and concomitant medications may exacerbate the problem.<sup>4,5,6,7</sup>

It often occurs early in treatment, can persist throughout treatment and may be dose-related although it has been reported in doses as low as 50mg.<sup>4</sup>

Clozapine may impair motility of the entire gastrointestinal system from the oesophagus to the rectum.<sup>6</sup> Every-Palmer *et al* (2016) measured colonic transit times (CTTs) of psychiatric inpatients treated with antipsychotics and found that 80% of clozapine-treated patients had hypomotility with CTTs four times longer than population norms and patients on other antipsychotics.<sup>8</sup>

### Risk factors for clozapine-induced gastrointestinal hypomotility

The following factors have been suggested to increase the risk of constipation in patients treated with clozapine.<sup>1,2,5,6</sup>

- Previous history of constipation, gastrointestinal disease or lower abdominal surgery
- Increasing age – patients aged 60 years and older may be particularly susceptible
- Concomitant use of other anticholinergic drugs
- Obesity
- Poor diet
- Low levels of exercise
- Poor bowel habit
- Higher clozapine dose or plasma level
- First 4 months of treatment
- Raised clozapine plasma levels caused by smoking cessation or cytochrome P450 enzyme-inhibiting drugs

It has also been suggested that fever, infection or inflammation may inhibit the metabolism of clozapine leading to increased plasma levels and risk of constipation.<sup>9,10</sup>

### Consequences of constipation

Clozapine-related constipation may reduce the patient's quality of life and lead to discontinuation of clozapine with subsequent deterioration in mental health. Very rarely patients may develop bowel obstruction, faecal impaction or paralytic ileus and on rare occasions such complications have been fatal.<sup>1,2</sup>

The risk of clozapine-induced constipation must not be underestimated. It is important to check that patients are not suffering from constipation and if it occurs it must be treated immediately with follow-up to ensure that the treatment has been effective.

Palmer *et al* (2008) reviewed 102 cases of suspected life-threatening clozapine-induced gastrointestinal hypomotility (CIGH) and found that patients were at risk regardless of age, sex, dose and duration of treatment.<sup>6</sup> The rate of mortality was 27.5% and there was significant morbidity mainly due to bowel resection.<sup>6</sup> Symptoms of serious pathology in the cases reviewed were moderate to severe pain, abdominal distension and vomiting with overflow diarrhoea, reduced appetite, nausea and septic shock cited as justification for urgent medical referral.<sup>6</sup>

## Management of clozapine-induced constipation

It is essential that constipation is recognized and managed immediately since if left untreated it can progress to intestinal obstruction, faecal impaction or bowel perforation. Accurate assessment of constipation is essential to determine the extent of the problem, other factors which may be exacerbating the situation and to exclude any complications.

Prior to the initiation of clozapine, patients and their carers should be warned about the risk of constipation and advised to seek medical attention immediately if it occurs.<sup>6</sup> Patients should be asked about their bowel function at each visit to the clinic and information given about preventative measures such as a high fibre diet, maintaining adequate fluids (especially if hypersalivation is a problem) and increasing activity levels.

Drugs such as tricyclic antidepressants, opioids and anticholinergics should be avoided if possible since they may exacerbate constipation. Consult your local clinical pharmacist for further information about drugs which may aggravate or cause constipation.

There are no specific guidelines on the treatment of clozapine-related constipation and insufficient data to support which laxatives are the most effective. A Cochrane Review (2017) concluded that there is inadequate evidence to assess drugs used to treat antipsychotic-related constipation in terms of safety and efficacy.<sup>11</sup>

For information on the management of constipation please refer to a medic, gastroenterologist or your local clinical pharmacist.

Some physicians will decrease the dose of clozapine if a patient develops constipation but, although worth considering, dose reduction may not be successful. In cases of severe constipation, where the patient's condition may be life-threatening, the treating team should consider withholding the clozapine.<sup>6</sup>

Patients who have an acute onset of symptoms, have severe symptoms, or who are unresponsive to treatment must be referred to a specialist for further investigation.

### References

1. Clozaril Summary of Product Characteristics (online). Mylan Products Limited. <http://www.medicines.org.uk/emc/> (Accessed on 04/07/2018).
2. Clozaril Summary of Product Characteristics (online). Mylan IRE Healthcare Limited. <http://www.medicines.ie/> (Accessed on 04/07/2018).
3. Hayes G and Gibler B. Clozapine-Induced Constipation. *American Journal of Psychiatry* 1995; **152**: 298
4. Chougule A *et al.* Prevalence and Factors Associated with Clozapine-Related Constipation. *Journal of Clinical Psychopharmacology* 2018; **1**: 42-46
5. Shirazi *et al.* Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis. *International Journal of Molecular Sciences* 2016; **17**(6).
6. Palmer SE *et al.* Life-Threatening Clozapine-Induced Gastrointestinal Hypomotility: An Analysis of 102 Cases. *J Clin Psychiatry* 2008; **69**: 759-768
7. Hibbard KR *et al.* Fatalities associated with clozapine-related constipation and bowel obstruction: a literature review and two case reports. *Psychosomatics* 2009; **50**: 416-419
8. Every-Palmer S *et al.* Clozapine-treated Patients have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications: A Cross Sectional Study. *EBioMedicine* 2016; **5**: 125-134
9. Raaska K *et al.* Bacterial pneumonia can increase serum concentration of clozapine. *Eur J Clin Pharmacol* 2002; **58**: 321-2.
10. Leung JG *et al.* Infection and inflammation leading to clozapine toxicity and intensive care: a case series. *Ann Pharmacother* 2014; **48**: 801-805.
11. Every-Palmer *et al.* Pharmacological Treatment for Antipsychotic-related Constipation. *Cochrane Library* 2017; Issue 1.

### Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

**UK:** Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

**Ireland:** HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: [www.hpra.ie](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie). Adverse events should also be reported to Mylan via [cpms@mylan.co.uk](mailto:cpms@mylan.co.uk)