Clozapine and gastrointestinal side-effects

**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.**

This information sheet will cover the following side-effects: nausea, vomiting, dysphagia, dry mouth and parotid gland enlargement. Constipation (including intestinal obstruction/paralytic ileus/faecal impaction) and hypersalivation are covered by separate information sheets.

**Nausea and vomiting**

The Summary of Product Characteristics (SmPC) of Clozaril® (clozapine) states that nausea and vomiting are common (≥1/100 but <1/10) side-effects. The mechanism is unclear and paradoxical (as antipsychotics can be expected to have antiemetic properties due to D₂ blockade). It may be due to the anticholinergic effect of delayed gastric emptying, increased salivation or to a centrally-mediated effect related to clozapine’s dopamine or serotonin activity. Onset of symptoms usually occurs within the first 6 weeks of treatment.

Tolerance often develops, however, the symptoms may be helped by decreasing the clozapine dose and titrating more slowly. Other successful treatments include the use of antacids or H₂ blockers, however, cimetidine should not be used as it may lead to increased clozapine plasma concentrations due to its inhibition of the P450 enzyme system. Antiemetics may also be used but it has been suggested that prochlorperazine and metoclopramide should be avoided due to the risk of extrapyramidal side-effects (EPSB).

The SmPC of Clozaril® recommends that liver function tests (LFTs) are performed on patients on clozapine who experience nausea, vomiting or anorexia as they are also possible signs of liver dysfunction. If the values are elevated to a level which is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with clozapine must be discontinued.

**Dysphagia**

Dysphagia is listed as a rare (≥1/10,000 but <1/1,000) side effect of Clozaril® in the SmPC. Psychiatric patients have been reported to have an increased incidence of dysphagia and choking (which may result in serious sequelae such as aspiration pneumonia or airway obstruction) compared to the normal population. The incidence of fatal asphyxia due to choking among psychiatric patients has been estimated at 0.85 per 1,000 per year, more than 100 times the incidence in the general population.

Possible causes include tardive dyskinesia, parkinsonism, anticholinergic effects of medications leading to impairment of the gag reflex, antidopaminergic effects of medications leading to direct impairment of the swallowing process, fast eating or gorging as a part of the psychiatric disorder or an unrelated medical illness.

Dysphagia may result in the aspiration of ingested food. Clozapine has both dopamine-blocking and anticholinergic properties and such effects may be responsible for some cases of dysphagia seen during clozapine treatment. Additionally, hypersalivation is a very common side-effect of clozapine and some cases of swallowing difficulties are attributed to sialorrhea.
Patient education regarding swallowing may help in cases of dysphagia. This may include teaching the patient to swallow using the correct posture and to eat more slowly with several swallows per bite.\textsuperscript{14} In addition, dose reduction has been reported to ameliorate symptomatic dysphagia.\textsuperscript{15}

**Dry mouth**

The SmPC of Clozaril\textsuperscript{®} states that dry mouth is a common (≥1/100 but <1/10) side-effect.\textsuperscript{1,2} Although hypersalivation is more commonly seen in patients on clozapine, dry mouth may occur as a result of the anticholinergic effect.

**Parotid gland enlargement**

Parotid gland enlargement is listed as a very rare (<1/10,000) side effect of Clozaril\textsuperscript{®} in the SmPC.\textsuperscript{1,2} Onset has generally been reported to occur within a few weeks of initiating treatment,\textsuperscript{16-18} although in one case it presented after approximately 10 months of treatment.\textsuperscript{17} In one publication the onset of swelling occurred during periods of dose increases.\textsuperscript{16} The mechanism is uncertain, but it has been suggested that it may be due to stasis of saliva or sustained hypersalivation, resulting in inflammation of the gland and/or formation of calculi which block the ducts.\textsuperscript{16,17} Both unilateral and bilateral enlargement has been reported in the literature and some cases were associated with a history of hypersalivation whilst others were not.\textsuperscript{16,17}

Submandibular swelling has also been described.\textsuperscript{16} The problem may resolve spontaneously\textsuperscript{16} (possibly due to the passage of a stone), in other cases anticholinergics may be helpful.\textsuperscript{17,18} For resistant cases referral to an ENT specialist may be required, however, many cases can be managed without the need to discontinue clozapine.\textsuperscript{16,17}

**Other gastrointestinal side-effects mentioned in the SmPC of Clozaril\textsuperscript{®}**

Diarrhoea, abdominal discomfort, heartburn, dyspepsia and colitis are also listed as adverse reactions which have a frequency of ‘not known’.\textsuperscript{1,2}

**References**