Clozaril® and urinary incontinence/urinary retention

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.

SmPC statement

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine)1,2 states that:

Urinary incontinence and urinary retention are common (≥1/100 but <1/10) side-effects of Clozaril®. Nocturnal enuresis is also listed as an adverse effect which has a frequency of ‘not known’.

Background

Urinary incontinence is known to be associated with severe mental illness and neuroleptic medications, including clozapine.3 While not usually a health risk, it is a major negative influence on a patient’s quality of life and can lead to non-compliance. It may occur at any time during clozapine treatment, at any dose and is frequently nocturnal. It has been reported in males and females of all ages,3 although the elderly may be particularly susceptible. Childhood enuresis has been identified as a risk factor, as has severity of mental illness, constipation, sedation, diabetes and seizures.3,4

The reported incidence in the literature ranges from around 2% up to around 40% (reported in one small case study evaluating 12 patients).3 There is evidence to suggest that it is often an under-reported side-effect due to the associated social stigma.3,4

Urinary retention may be serious enough to require emergency treatment.5,6 Patients at most risk of developing retention are those with pre-existing conditions that involve incomplete voiding of the bladder, such as prostatic enlargement.7 Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of Clozaril.1,2

Mechanism

There are a number of possible mechanisms that can explain the occurrence of urinary retention and incontinence. The potent anticholinergic activity of clozapine may result in urinary retention with subsequent overflow resulting in incontinence.

It has also been proposed that the antiadrenergic activity of clozapine decreases bladder sphincter tone and causes bladder emptying. Urinary disorders may also occur as a secondary consequence of other disorders or side-effects associated with clozapine, for example, incontinence may be secondary to excessive sedation which then prevents the patient from waking during sleep to empty the bladder. Clozapine-induced constipation may aggravate urinary retention resulting in secondary overflow, and incontinence secondary to diabetes and seizures may also occur.3,4
**Prevention**

It may be necessary to enquire specifically about incontinence since there is evidence to show that patients are reluctant to report what they see as an embarrassing side-effect.

Urinary incontinence often occurs at night (nocturnal enuresis) and it may be helpful to restrict fluids during the evening and make sure that patients urinate before going to bed. Patients should have easy access to a toilet and, in addition, it may be worth waking the patient during the night to use the toilet. Another consideration is to reduce the clozapine dose or alter the dosage schedule, reducing the evening dose to avoid deep sedation.

Due to the severity of urinary retention, it is recommended that elderly patients and those with prostatic enlargement or other pre-existing conditions that involve incomplete voiding of the bladder, are carefully supervised. Constipation in patients on clozapine should be identified and managed due to the risk of developing gastrointestinal obstruction, in addition to the aggravation of retention.

Other drugs with anticholinergic or sedative side-effects should be avoided where possible.

**Management**

Urinary incontinence, as mentioned above, may be secondary to constipation, seizures or diabetes mellitus and it is important to distinguish and manage the underlying cause prior to initiating any treatment.

It is also important to ensure that urinary retention is excluded before treating the patient for urinary incontinence.

Some cases of urinary incontinence may resolve spontaneously.

For pharmacological treatment, please check local hospital trust guidelines on effective drug management of urinary incontinence.

Urinary retention should be managed in consultation with a urologist. Acute retention may require emergency catheterisation and hospital admission.

**References**

Switching from a previous antipsychotic therapy to Clozaril is mandatory if either the WBC count is less than 3.0x10^9/l or the ANC is less than 1.5x10^9/l at any time during Clozaril treatment. Patients in whom Clozaril has been associated with an increased risk of myocarditis and cardiomyopathy. If suspected Clozaril must be stopped immediately and the patient referred to a cardiologist and not re-exposed to Clozaril.

Presentations
Clozaril 25 mg Tablets containing 25 mg clozapine. Clozaril 100 mg Tablets containing 100 mg clozapine.

Indications
Treatment-resistant schizophrenic patients and in schizophrenia patients with severe, unremitting neurological adverse reactions to other antipsychotic agents, including an atypical antipsychotic agent prescribed for adequate duration. Psychotic disorders occurring during the course of Parkinson’s disease, where standard treatment has failed.

Dosage and Administration
Treatment-resistant schizophrenic patients
12.5 mg once or twice on the first day, followed by 25 mg tablets once or twice on the second day. Increase dose slowly, by increments (see SmPC). In most patients, antipsychotic efficacy can be expected with 200 to 450 mg by an equal divided doses. If dose does not exceed 200 mg/day, it can be given as a single administration in the evening. Once control is achieved, lower maintenance dose may be effective. Treatment should be maintained for at least 6 months. Doses up to 900 mg/day can be used but the possibility of increased adverse reactions (especially seizures) occurring at doses over 450 mg/day must be considered.

Method of administration
Clozaril is administered orally.

Contraindications
Hypersensitivity to the active substance or to any of the excipients. Patients unable to undergo regular blood tests. History of toxic or idiosyncratic granulocytopenia /agranulocytosis (with the exception of granulocytopenia /agranulocytosis from previous chemotherapy). Patients with pre-existing liver disease (e.g. cirrhosis).

Warnings and Precautions
Agranulocytosis: Before initiating clozapine therapy, patients should have a blood test and a history and physical examination. Clozaril can cause agranulocytosis, so is restricted to patients who have initially normal leukocyte findings. White Blood Cell (WBC) count > 3.5x10^9/l and Absolute Neutrophil Count (ANC) > 2.0x10^9/l, and in whom regular WBC counts and ANC can be performed within 10 days prior to starting Clozaril, weekly for first 18 weeks, thereafter at 4 week intervals throughout treatment and for 4 weeks after complete discontinuation. Patients with history of cardiac illness or abnormal cardiac findings on physical examination prior to treatment should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG. QT interval prolongation: As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation. As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QT interval. Pre-existing or new cardiac disease: Patients should be treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG.

Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation. Blood clozapine level monitoring is advised in situations such as a patient ceases smoking or switches to e-cigarettes, when concomitant medicines may interact to increase clozapine blood levels, where poor clozapine metabolism is suspected, when a patient has pneumonia or other serious infection and in the event of onset of symptoms suggestive of toxicity. Clozaril is associated with an increased risk of myocarditis and cardiomyopathy. If suspected Clozaril must be stopped immediately and the patient referred to a cardiologist and not re-exposed to Clozaril.
Eosinophilia: Discontinuation of Clozaril is recommended if the eosinophil count rises above 3.0x10^9/l; therapy should be restarted only after the eosinophil count has fallen below 1.0x10^9/l.

Discontinuation of Thrombocytopenia: Clozaril therapy is recommended if the platelet count falls below 50x10^9/l. Cardiovascular disorders: Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest which is more likely to occur with concurrent use of certain medications (see SPC for more details) and during initial titration with rapid dose escalation. Patients starting Clozaril treatment require close medical supervision. Clozaril is associated with an increased risk of myocarditis, pericarditis/pericardial effusion and cardiomyopathy; and if suspected, Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist. Patients with clozapine induced myocarditis or cardiomyopathy should not be re-exposed to Clozaril. In patients who are diagnosed with cardiomyopathy while on Clozaril treatment, there is potential to develop mitral valve incompetence, including mild or moderate mitral regurgitation. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure or symptoms mimicking myocardial infarction. If such symptoms may also be present, Myocardial Infection Test (MIT) should be performed. Patients with a history of epiplegy should be closely observed during Clozaril therapy since dose related convulsions have been reported.

Neuropsychiatric: Patients with stable pre-existing liver disorders or liver dysfunction need to be monitored carefully. Activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Interaction with other medicinal products and other forms of interaction

Clozaril must not be used concomitantly with substances having a well-known potential to suppress bone marrow function. (See Section 4.3 of the SmpC, Contraindications).

Long-acting depot antipsychotics (with noresponsive potential) must not be used with Clozaril because these cannot be removed from the body in situations where they may be required e.g. neuronephrosis. Alcohol should not be used with Clozaril due to possible potentiation of sedation.

Caution is advised if Clozaril is used concurrently with other CNS active agents such as, MAOIs, perazine, SSRIs especially fluoxetine, caffeine, CNS depressants including narcotics, antihistamines and benzodiazepines. Caution is advised if Clozaril is used concurrently with antiparkinsonian agents, highly protein bound drugs (e.g. warfarin and digoxin), phenytoin, lithium, trimipramine, tubocurarine, haloperidol, chlorpromazine, propranolol, pindolol, and theophylline. Concurrent use of clozapine with products that are substrates (such as azole antifungals), inhibitors (such as ketoconazole) or inducers (such as phenytoin) of CYP3A4 may result in substantial changes in the plasma clozapine concentration which may increase, decrease or be unaffected.

Fertility, Pregnancy and Lactation

Pregnancy: Caution should be exercised when prescribing to pregnant women. Neonates exposed to antipsychotics (including Clozaril) during the third trimester are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully. Activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Fertility: Limited data available on the effects of clozapine on human fertility are inconclusive.

Women of child-bearing potential: A return to normal menstruation may occur as a result of switching from other antipsychotics to Clozaril. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Ability to Drive and Operate Machinery

Owing to the ability of Clozaril to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Undesirable effects

Adverse reactions are ranked under headings of frequency. Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (≥1/100,000, <1/10,000), including isolated report.

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever.

Very common: Drowsiness/sedation, dizziness, tachycardia, constipation, hyperpyrexia.
Common: Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis, weight gain, blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures, convulsions, psychotic jju, ECG changes, hypertension, postural hypotension, syncope, nausea, vomiting, anorexia, dry mouth, elevated liver enzymes, urinary incontinence, urinary retention, fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation, dysphoria.
Uncommon: Agranulocytosis, neuroleptic malignant syndrome, dysphoria, falls.
For details of rare, very rare and not known undesirable effects please refer to SmpC.

Package Quantities and basic NHS price
28 x 25 mg tablets: £2.95; 84 x 25 mg tablets: £6.30; 100 x 25 mg tablets: £7.50
28 x 50 mg tablets: £41.76; 84 x 100 mg tablets: £320.01
Supply of Clozaril is restricted to hospital pharmacies registered with the CLOZARIL Patient Monitoring Service.

Marketing Authorisation Holder
Violaris Limited, 20 Station Close, Potters Bar, Herts, EN6 1TL, UK.

Product Authorisation Numbers
25 mg tablets: PL 232354
100 mg tablets: PL 46302/0057

Legal Category: POM

Further information available in the UK from: BGP Products UK Ltd., Building O1, Quantum House, 60 Norden Road, Maidenhead, Berkshire, SL6 4AY, UK.

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