Clozapine, diabetes and hyperglycaemia

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 (SmPC) for Clozaril® (clozapine) states that diabetes mellitus and impaired glucose tolerance are rare (≥1/10,000 but <1/1,000) side effect.1,2 Ketoacidosis, hyperosmolar coma and severe hyperglycaemia are listed as very rare (<1/10,000).1,2

Metabolic changes

Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific profile.1,2

Hyperglycaemia

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined. Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycaemia, some of which have been fatal. When follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its reoccurrence. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing.1,2

In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.1,2

Dyslipidaemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including clozapine. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.1,2

Metabolic and nutritional disorders

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported in patients on Clozaril® treatment with no prior history of hyperglycaemia. Glucose levels normalised in most patients after discontinuation of Clozaril® and in a few cases hyperglycaemia recurred when treatment was reinitiated. Although most patients had risk factors for non-insulin-dependent diabetes mellitus (NIDDM), hyperglycaemia has also been documented in patients with no known risk factors.1,2
Both diabetes and hyperglycaemia have been reported with a higher overall prevalence in both untreated and (even more so) treated schizophrenia as compared to the general population.3-6

Risk factors

Most, although not all, patients that develop diabetes or impaired glucose tolerance whilst on antipsychotics have risk factors for NIDDM. Important general risk factors include past medical or family history, male gender, obesity and lack of physical activity.7 Physical inactivity may be particularly relevant in clozapine patients due to the sedating properties of clozapine. Patients aged 40 or over and people from an Afro-Caribbean or Indo-Asian background also have a greater risk of developing NIDDM.

Prevention and monitoring

Before starting clozapine it is advisable that patients should be assessed with respect to risk factors for impaired glucose tolerance and diabetes, though this is not a mandatory requirement.

Routine glucose monitoring again is not mandatory. If it is carried out as part of good clinical practice, it is a clinical decision how often the test should be performed.

Management and re-challenge

It is very important to recognise impaired glucose tolerance and diabetes early. The possibility should be considered in any patient receiving clozapine who develops symptoms of hyperglycaemia, such as polydipsia or polyuria, and the patient referred for assessment of their condition. Management advice should be sought from the medical team if necessary.

If ketoacidosis or hyperosmolar coma develop clozapine should be stopped immediately and the patient admitted to a medical ward. Re-challenge in these patients should be done cautiously and with careful monitoring of the patient’s glucose levels.

References


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

Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medicsafety@hpra.ie

Adverse events should also be reported to Mylan via cpms@mylan.co.uk