Clozapine and fever

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 of Clozaril® (Clozapine) states that fever and benign hyperthermia are a common (≥1/100 but <1/10) side effect.¹ ²

During Clozaril® therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. If the diagnosis of NMS is confirmed, Clozaril® should be discontinued immediately and appropriate medical measures should be administered.¹ ²

Fever or benign transient hyperthermia (temporary elevation of temperature without serious effects) generally involves an increase in temperature of 0.5-1°C,⁴ is often spiking in nature⁵ and is of no clinical significance, resolving spontaneously over a few days.

Although fever in clozapine-treated patients is not usually significant it is important to consider the possibility of more serious conditions such as agranulocytosis, myocarditis, neuroleptic malignant syndrome or an underlying infection. If necessary the clozapine should be withheld until these are excluded. Please see the neutropenia and agranulocytosis, cardiovascular events or neuroleptic malignant syndrome factsheets respectively for more information about management of these conditions.

The incidence of fever in clozapine-treated patients reported in the literature varies considerably from 1.2% up to as much as 55%,³⁵-¹⁰ although this wide variation may be due to the different thresholds used to define fever.

The fever may be associated with tachycardia or gastrointestinal or respiratory symptoms,¹¹ or an elevated white blood cell count (WBC).⁵ ¹² Increases in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have also been reported.⁹

With respect to risk factors, clozapine-induced fever is not dose-related¹³ and the incidence does not appear to be affected by gender, although older patients may be at more risk.⁵
Management

It is a clinical decision for the treatment team to stop clozapine if a patient develops a fever. It is important to investigate for all possible causes of fever and treat the underlying cause if necessary.

Most cases of clozapine-induced fever resolve spontaneously, however, whenever a patient on clozapine presents with a raised temperature a full blood count with differential must be undertaken to ensure that the patient does not have an underlying neutropenia. The occurrence of neutropenia at such an early stage in treatment would be unusual, however, it is essential that the count is checked. If the patient is neutropenic clozapine must be stopped immediately.

References

Report 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, Earliston Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie
Adverse events should also be reported to Mylan via cpms@mylan.co.uk