

Clozapine and benign ethnic neutropenia

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:

Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may only be started on Clozaril[®] with the agreement of a haematologist.

Background

Benign ethnic neutropenia (BEN) can be defined as: 'The occurrence of neutropenia, defined by normative data in white populations, in individuals of other ethnic groups who are otherwise healthy and who do not have repeated or severe infections'.³

It has also been called pseudoneutropenia, benign familial neutropenia, nongenetic neutropenia, 'benign' neutropenia of the black, familial neutropenia, benign hereditary neutropenia, benign hereditary leucopenia-neutropenia, benign familial leucopenia and neutropenia, and chronic benign idiopathic neutropenia.^{3,4}

BEN is the most common form of neutropenia in the world³ occurring in 25-50% of people of African descent³. It also occurs in a number of Jewish, Middle Eastern and Afro-Caribbean groups.^{3,4,5}

BEN is thought to be due to a defect in the release of mature white cells from the bone marrow to the peripheral circulation.⁴ It causes low leucocyte and neutrophil counts³ and neutropenia can be seen without leucopenia.⁴

Are patients with BEN at increased risk of infection?

The susceptibility to infections in this group of patients is not believed to be increased.⁴ The response to infection appears to be normal and the outcome of infections appears to be no worse than control groups.⁴

Clozaril[®] Patient Monitoring Service (CPMS) data have shown that, although Afro-Caribbeans and Africans are significantly more likely than other ethnic groups to have both pre-treatment and on-treatment neutropenia, they are not at an increased risk of agranulocytosis.^{6,7}

Diagnosis

There is no definitive diagnostic test for BEN. It is a diagnosis made on clinical judgement. As necessary, the local haematologist should be consulted to see if a patient has a BEN diagnosis.

CPMS management of patients with BEN

The CPMS has historically agreed a set of alternative monitoring criteria for these patients. The aim is to minimise disruption to therapy resulting from a normal variant, without compromising patient safety.

Traditional CPMS Alert Ranges (Normal blood monitoring)

Alert Colour	WBC x 10 ⁹ /L	Neutrophils x 10 ⁹ /L
Green	>3.5	>2.0
Amber	3.0 – 3.5	1.5 – 2.0
Red	<3.0	<1.5

BEN CPMS Alert Ranges

Alert Colour	WBC x 10 ⁹ /L	Neutrophils x 10 ⁹ /L
Green	>3.0	>1.5
Amber	2.5 – 3.0	1.0 – 1.5
Red	<2.5	<1.0

As shown above, the ranges differ by 0.5 x 10⁹/L.

Any patients who develop a red or amber alert within the modified ranges will be treated as per standard CPMS procedures.

Registering BEN patients with the CPMS

For a patient to be registered with the CPMS with the BEN monitoring criteria, a letter is required from the registered consultant psychiatrist confirming that a haematologist has agreed to a probable diagnosis of BEN.

References

1. Clozaril Summary of Product Characteristics (online). Mylan Products Limited. <<http://www.medicines.org.uk/emc/>> (Accessed on 02/04/2018).
2. Clozaril Summary of Product Characteristics (online). BGP Products Ireland Limited. <<http://www.medicines.ie/>> (Accessed on 02/04/2018).
3. Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med* 1999; **133**(1): 15-22.
4. Shoenfeld Y *et al.* Benign familial leukopenia and neutropenia in different ethnic groups. *Eur J Haematol* 1988; **41**(3): 273-277.
5. Bain BJ. Ethnic and sex differences in the total and differential white cell count and platelet count. *J Clin Pathol* 1996; **49**(8): 664-666.
6. Atkin K *et al.* Neutropenia and Agranulocytosis in Patients Receiving Clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169**: 483-488.
7. Munro J *et al.* Active monitoring of 12760 clozapine recipients in the UK and Ireland. *Br J Psychiatry* 1999; **175**: 576-580.

Adverse events should be reported.

For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

For Ireland, report adverse events via HPRA Pharmacovigilance medsafety@hpra.ie.

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