Pharmacology and toxicology

Clozapine, agranulocytosis, and benign ethnic neutropenia

S Rajagopal

Current knowledge and clinical implications

Clozapine is an atypical antipsychotic that is effective in treatment resistant schizophrenia.[1] The National Institute for Health and Clinical Excellence (NICE) guidelines for schizophrenia specify that ''in individuals with evidence of treatment resistant schizophrenia, clozapine should be introduced at the earliest opportunity''.[2]

A severe adverse effect of clozapine that limits its more widespread use is agranulocytosis. Patients who are taking clozapine need to have their full blood counts (FBC) monitored regularly, and if the total white cell and/or neutrophil counts indicate agranulocytosis, clozapine prescription must be terminated. Among certain ethnic groups, a significant proportion of people have a low baseline neutrophil count. This is called benign ethnic neutropenia (BEN). This editorial looks at the important issues associated with agranulocytosis and BEN in patients receiving clozapine.

CLOZAPINE AND AGRANULOCYTOSIS

Agranulocytosis occurs in about 1% of patients taking clozapine.[3 4] Neutropenia is seen in about 3%.[4] The risk of both agranulocytosis and neutropenia is highest between 6 weeks and 18 weeks after starting clozapine treatment.[4] Hence, in the United Kingdom and Ireland, weekly FBC monitoring is mandatory for the first 18 weeks, after which it is done fortnightly until the end of the first year, and every four weeks thereafter. In the USA, FBC is monitored weekly for the first six months and fortnightly thereafter.

Not all risk factors are the same for agranulocytosis and neutropenia; this implies that there may be distinct mechanisms for the two disorders. A low baseline white cell count has been associated with future neutropenia but not agranulocytosis.[5] The risk of agranulocytosis increases with age,[3 6] while that of neutropenia decreases with age.[6] Agranulocytosis is more common in women.[3] It is more than twice as frequent in Asians as in the white population.[6] Neutropenia, but not agranulocytosis, is more common in black people.[6] A white cell count spike of 15% or more above the immediately preceding measurement may predict agranulocytosis within the next 75 days.[7] However, as these differences between the risk factors for agranulocytosis and neutropenia have been extrapolated primarily from epidemiological studies, they may be subject to change as further evidence, from even larger studies, come to light.

The exact mechanism of clozapine induced agranulocytosis is unclear. It has been postulated that clozapine is metabolised to a nitrenium ion.[8] The binding of this ion to neutrophils may result in agranulocytosis. Antineutrophil antibodies may be involved in mediating agranulocytosis.[9] Some human leucocyte antigen (HLA) alleles, for example the HLA B38 phenotype in Ashkenazi Jews,[10] have been shown to be associated with clozapine induced agranulocytosis.

OTHER HAEMATOLOGICAL ABNORMALITIES

Clozapine is associated with increased risk of eosinophilia, particularly in women.[11] Eosinophilia typically occurs between weeks 3 and 5 of treatment and resolves spontaneously without need for specific treatment. Clozapine is also associated with anaemia, lymphopenia, leucocytosis, and thrombocytopenia.[8]

BENIGN ETHNIC NEUTROPENIA

BEN has been 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''.[12] About 25% to 50% of Africans and some ethnic groups in the Middle East, including Yemenite Jews and Jordanians, have BEN.[12 13] BEN has only been reported in ethnic groups that have tanned or dark skin.[13] Subjects with BEN do not show increased incidence of infections, and their response to infections is similar to those without BEN.[13]

CLINICAL IMPLICATIONS

In the United Kingdom and Ireland, the Clozaril patient monitoring service (CPMS) supervises the prescribing of clozapine and the haematological testing (Clozaril is the brand name of clozapine). The CPMS uses a lower cut off point for patients with BEN than for the general population (table 1). A ''green'' alert indicates satisfactory count, an ''amber'' alert requires a repeat FBC test while clozapine can be continued, and a ''red'' alert warrants immediate cessation of clozapine.

It is important for eligible subjects to be registered with the CPMS under the BEN category, so that patients belonging to certain ethnic groups do not have to stop clozapine unnecessarily. This has great clinical ramifications, as there is no other antipsychotic that has comparable efficacy to clozapine in the treatment of resistant schizophrenia. In addition, there is evidence that some ethnic groups, particularly black people, may be less likely, even in the first place, to be prescribed clozapine.[14] These factors may combine to further worsen the prognosis of an already severely debilitating illness in this group of patients.

As clozapine induced agranulocytosis is an idiosyncratic reaction,[8] it is difficult to predict and to identify high risk patients. Also, as it is a comparatively rare phenomenon occurring in less than 1% of subjects, the number of reported cases is not adequate to clearly identify specific risk factors; general risk factors such as increasing age, female sex, etc, are not robust enough to change decision making in individual patients. Therefore, clinicians should continue to remain vigilant against this potentially fatal side effect of clozapine in all the patients prescribed this drug, especially in the first few months of treatment.

ACKNOWLEDGEMENTS

Dr Tony Wong, staff grade psychiatrist, South London and Maudsley NHS Trust.

Table 1 CPMS alert ranges for subjects with BEN (ranges for non-BEN subjects)

Alert colour	WCC $\times 10^9$/l	Neutrophils $\times 10^9$/l
Green	>3.0 (>3.5)	>1.5 (>2.0)
Amber	2.5–3.0 (3.0–3.5)	1.0–1.5 (1.5–2.0)
Red	<2.5 (<3.0)	<1.0 (<1.5)

CPMS, Clozaril patient monitoring service; BEN, benign ethnic neutropenia; WCC, white cell count.

Postgrad Med J 2005;**81**:545–546.
doi: 10.1136/pgmj.2004.031161

Correspondence to: Dr S Rajagopal, South London and Maudsley NHS Trust, Adamson Centre for Mental Health, St Thomas's Hospital, London SE1 7EH, UK; Sundararajan.Rajagopal@slam.nhs.uk

Funding: none.

Competing interests: none.

REFERENCES

1 **Kane J**, Honigfeld G, Singer J, *et al.* Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;**45**:789–96.
2 **National Institute for Clinical Excellence**. *Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. Clinical guideline 1*. London: NICE, 2002.
3 **Alvir JM**, Lieberman JA, Safferman AZ, *et al.* Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med* 1993;**329**:162–7.
4 **Atkin K**, Kendall F, Gould D, *et al.* Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996;**169**:483–8.
5 **Gillman K**. Paradoxical pattern of haematological risk with clozapine. Authors' reply. *Br J Psychiatry* 2000;**177**:88.
6 **Munro J**, O'Sullivan D, Andrews C, *et al.* Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *Br J Psychiatry* 1999;**175**:576–80.
7 **Alvir JM**, Lieberman JA, Safferman AZ. Do white-cell count spikes predict agranulocytosis in clozapine recipients? *Psychopharmacol Bull* 1995;**31**:311–14.
8 **Pirmohamed M**, Park K. Mechanism of clozapine-induced agranulocytosis. Current status of research and implications for drug development. *CNS Drugs* 1997;**7**:139–58.
9 **Claas FH**. Drug-induced agranulocytosis: review of possible mechanisms, and prospects for clozapine studies. *Psychopharmaclogy (Berl)* 1989;**99**(suppl):S113–17.
10 **Meged S**, Stein D, Sitrota P, *et al.* Human leukocyte antigen typing, response to neuroleptics, and clozapine-induced agranulocytosis in jewish Israeli schizophrenic patients. *Int Clin Psychopharmacol* 1999;**14**:305–12.
11 **Banov MD**, Tohen M, Friedberg J. High risk of eosinophilia in women treated with clozapine. *J Clin Psychiatry* 1993;**54**:466–9.
12 **Haddy TB**, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med* 1999;**133**:15–22.
13 **Shoenfeld Y**, Alkan ML, Asaly A, *et al.* Benign familial leukopenia and neutropenia in different ethnic groups. *Eur J Haematol* 1988;**41**:273–7.
14 **Kuno E**, Rothbard AB. Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. *Am J Psychiatry* 2002;**159**:567–72.

Single subject design

Should the single subject design be regarded as a valid alternative to the randomised controlled trial?

R G Newcombe

For debate.

In an accompanying article Janine Janosky sets out the case for the use of single subject designs.[1] I was asked by my colleague Dr John Mayberry, the editor of the journal, to referee this paper, but felt it would be more appropriate to respond to it, largely to stimulate debate on this issue. I would suggest that the proper applicability of single subject designs is much narrower than this article would imply. I would furthermore warn readers of the dangers of a view that if left to grow unchecked could result in an important undermining of the dominance of the multi-patient randomised clinical trial that is now, with very strong justification, accepted as the cornerstone of evidence based clinical practice—with serious consequences for the choice of appropriate management for future patients. The two key issues are equivocation regarding the ambit of the single subject design, and the robustness of the inference to be drawn from data such as figure 1 in Janosky's paper.

It is well accepted that clinical expertise is needed to apply the findings of large clinical trials to the individual patient. The doctor's initial training, ongoing CPD, and clinical experience facilitate the recognition of patients who are not ''average'' and for whom current evidence based guidelines, which are optimised for patient populations, may not be optimal. How to decide on management for a specific patient may be problematic. When the issue relates to maintenance treatment, the single patient design certainly has a role. For example, the patient may have two coexisting conditions for which the therapeutic requirements conflict. Another context is polypharmacy—perhaps the patient is currently taking four drugs, and the clinician suspects that one could be withdrawn without diminution of therapeutic effect.

In some parts of the article, including the six listed ''possible research questions'', Dr Janosky clearly implies that the research issue only applies to a specific patient. In other places, a broader scope is implied by phrases such as ''unique study populations'', ''choosing the patient to participate'', and ''typical in terms of the practice demographics (and) for disease presentation and progression''. Dr Janosky concedes that there is an issue of limited generalisability. I would argue that a study of this kind cannot provide any reassurance that we can extrapolate the findings to other patients. One could say, to other similar patients, but what does similar mean in this context? Demographic, physiological, and diagnostic similarity are of little relevance here, the only similarity that matters relates to propensity to respond to the treatment in question, and this can neither be observed nor ensured. Conversely, the conventional large clinical trial relates to patients drawn from a population defined by well defined eligibility criteria, and random allocation ensures groups are comparable within limits of chance variation in respect of all possible variables, including counterfactual treatment response. This is what justifies applying the conclusions of the trial to patients at large who fulfil the eligibility criteria used in the trial.

The other key issue relates to drawing an ''obvious'' conclusion from a limited dataset. This is shaky on two counts, relating to clinical lability and statistical methodology. Dr Janosky refers to the patient ''in need of lower fasting blood glucose values''—but there is such a thing as regression towards the mean (strictly, a misnomer, regression towards the mode would be a more apt description). The inference that the ''switch'' in figure 1 is real is strongly dependent on a presupposition that patients don't just ''switch'' spontaneously in this way. Perhaps this is reasonable in diabetes—it would not be for remitting/relapsing conditions such as inflammatory bowel disease or multiple sclerosis, and certainly not for thyroid disease or bipolar disorder. What Dr Janosky terms the ''primary A-B single subject design'', as used here,