Correspondence

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Clozapine treatment following blood dyscrasia

Dunk *et al* (2006) investigated 53 patients who were rechallenged with clozapine following leucopenia or neutropenia during previous therapy and found that 33 did not experience a second episode of blood dyscrasia and were able to continue drug treatment. This result is of considerable clinical relevance because it suggests that some patients with leucopenia or neutropenia may unnecessarily be denied effective clozapine treatment.

We agree that there may be two types of clozapine-associated neutropenia: an early sign of incipient agranulocytosis and a more common transient and harmless phenomenon, not necessitating the discontinuation of drug treatment. Transient neutropenia (defined as a return of the neutrophil count to normal values without changing the clozapine dosage) was found in 22% of 68 patients treated with clozapine for the first time (Hummer *et al*, 1994). Neutropenia of short duration (2–5 days) and weekly benign variations of the neutrophil count have been reported. Marked circadian variations in the number of circulating neutrophils (morning pseudoneutropenia) have also been described in several clozapine-treated patients (Ahokas & Elonen, 1999; Esposito *et al*, 2004).

The actual issue might therefore not be which patients could be rechallenged with clozapine following drug-associated neutropenia but which could be maintained on clozapine despite this side-effect. Laboratory screening tests, including the use of a hydrocortisone test, are being devised to determine whether clozapine-associated neutropenia is transient or malignant (Murry & Laurent, 2001). Until these tests become available for routine use, it is necessary to increase the frequency with which white blood cell counts are determined. As first suggested by Ahokas & Elonen (1999), when the absolute neutrophil count is below the normal range in the morning, the test should be repeated in the afternoon of the same day before a decision to stop clozapine treatment is made. This might be the basis for further clarification of the significance of transient neutropenia.

Ahokas, A. & Elonen, E. (1999) Circadian rhythm of white blood cells during clozapine treatment. *Psychopharmacology*, **144**, 301–302.

Dunk, L. R., Annan, L. J. & Andrews, C. D. (2006) Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. *British Journal of Psychiatry*, **188**, 255–263.

Esposito, D., Aouille, J., Rouillon, F., *et al* (2004) Two-year follow-up of a patient with successful continuation of clozapine treatment despite morning pseudoneutropenia. *Journal of Clinical Psychiatry*, **65**, 1281.

Hummer, M., Kurz, M., Barnas, C., *et al* (1994) Clozapine-induced transient white blood count disorders. *Journal of Clinical Psychiatry*, **55**, 429–432.

Murry, P. & Laurent, A. (2001) Is it possible to distinguish between benign and malignant neutropenia in clozapine-treated patients by means of a hydrocortisone test? *Psychopharmacology*, **158**, 329–330.

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Authors' reply: We agree that attempts should be made to continue patients on clozapine if at all possible in order to give them an adequate trial of the drug. The Clozaril Patient Monitoring Service (CPMS) routinely advises that samples should not be taken first thing in the morning for patients with borderline white cell/neutrophil counts to avoid the problem of morning pseudoneutropenia. Taking samples after a brisk walk has also been suggested in such patients.

Although Hummer *et al* (1994) reported transient neutropenia in 22% of 68 patients they defined leucopenia as a white cell count $<3.5\times10^9$/l and neutropenia as a neutrophil count $<2.0\times10^9$/l. The mean neutrophil count at the time of the transient neutropenia was 1.78×10^9/l. In the UK and generally, the cut-off points for leucopenia and neutropenia used in clozapine monitoring are lower (3.0×10^9/l and 1.5×10^9/l respectively) and patients with counts higher than this are not required to stop clozapine but are monitored more frequently. The relevance of the findings of the study to all clozapine-treated patients must therefore be considered with this point in mind.

The use of a hydrocortisone test to distinguish between benign and malignant neutropenia is of great interest but findings must be interpreted with caution as the study involved only three patients (Murry & Laurent, 2001). Furthermore, the risk of further stressing a compromised bone marrow must be borne in mind with such interventions. Whether it is possible to distinguish between transient neutropenia and the prelude to agranulocytosis in clozapine-treated patients remains to be determined.

Declaration of interest

L.D. has undertaken consultancy for Novartis UK and Novartis Australia and received a fee from Novartis Australia for the preparation of the paper; she was formerly employed by Novartis UK. L.A. and C.A. are employed by Novartis UK.

Hummer, M., Kurz, M., Barnas, C., *et al* (1994) Clozapine-induced transient white blood count disorders. *Journal of Clinical Psychiatry*, **55**, 429–432.

Murry, P. & Laurent, A. (2001) Is it possible to distinguish between benign and malignant neutropenia in clozapine-treated patients by means of a hydrocortisone test? *Psychopharmacology*, **158**, 329–330.

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Personality disorder and outcome in depression

Newton-Howes *et al* (2006) attempted to definitively answer the question of whether comorbid personality disorder affects outcome in people with major depression. Their search strategy, study selection, data summary and analysis are clearly described.