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Managing clozapine-induced neutropenia with lithium

AIMS AND METHOD

To review the efficacy and safety of lithium augmentation for the management of clozapine-induced neutropenia. Medline search January 1966 to March 2004.

RESULTS

The ability of lithium to increase the white cell count (WBC) is well documented. A small number of published case reports of the successful treatment of clozapine-induced neutropenia with lithium were identified. Lithium does not protect against agranulocytosis.

CLINICAL IMPLICATIONS

Lithium may be useful in raising the WBC in patients whose baseline count is too low to allow treatment with clozapine to start and to protect against clozapine-induced neutropenia, thus allowing more patients to benefit from treatment with clozapine. It does not protect against agranulocytosis. There is no way of identifying patients whose neutropenia will progress to agranulocytosis. Careful monitoring is essential. Lithium is not licensed to increase WBC. Psychiatrists should be aware of the medicolegal implications of prescribing off-label.

It is estimated that approximately 30% of patients with schizophrenia respond poorly to typical and atypical antipsychotic drugs and warrant treatment with clozapine (National Institute for Clinical Excellence, 2002). Clozapine is a uniquely effective drug in patients with 'treatment resistant' illness and its use can lead to significant improvements in mental state and quality of life for patients (Iqbal *et al*, 2003). It is therefore imperative that as many eligible patients as possible are offered treatment with this drug.

Method

We conducted a Medline search for the period covering January 1966 to March 2004, using the terms CLOZAPINE, LITHIUM, NEUTROPENIA *and* AGRANULOCYTOSIS. Papers covering the effect of lithium on the white cell count (WBC) and the use of lithium to increase the WBC in patients treated with clozapine were retrieved.

Results

Neutropenia and agranulocytosis

Clozapine can cause neutropenia and agranulocytosis. In the UK, the Clozaril Patient Monitoring System (CPMS) was set up to ensure patients receive regular haematological monitoring and so prevent deaths from agranulocytosis. In order to start treatment with clozapine, patients must have a baseline total WBC of $>4\times10^9$/l and a neutrophil count of $>2.5\times10^9$/l. Haematological results are reported as 'green' (safe to continue treatment), 'amber' (borderline low or falling result) and 'red' (below the acceptable reference range). If the WBC subsequently drops below the 'red' cut-off of 3×10^9/l or the neutrophil count falls below 1.5×10^9/l, clozapine treatment must be stopped. This monitoring system has been extremely successful in preventing deaths secondary to agranulocytosis, but is seen by some clinicians as being very rigid and taking clinical decisions out of the hands of clinicians (Beer *et al*, 1994). The CPMS has responded to these concerns by introducing slightly lower reference ranges for patients with benign ethnic neutropenia; this is a welcome development. Some patients however continue to have a WBC that hovers just above the 'red' range. In such patients, a tiny drop in WBC may result in the patient having to stop treatment. Lack of exercise, having not smoked a cigarette or simply having blood taken at the wrong time of day (Abramson & Melton, 2000) could result in clozapine treatment having to be stopped. The consequences for the patient can be significant.

Quantifying the risk of neutropenia and agranulocytosis

Data from the CPMS reveal that 0.4% of patients had a pre-treatment WBC that was too low to allow treatment with clozapine to be initiated. In 75% of cases, the patient was of African or African–Caribbean origin (Atkin *et al*, 1996).

In addition to the above 'baseline rate', just under 3% of patients treated with clozapine develop neutropenia. Of these, half do so within the first 18 weeks of

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treatment and three-quarters by the end of the first year (Munro *et al*, 1999). Risk factors include being African–Caribbean (77% increase in risk), young (17% decrease in risk per decade increase in age) and having a low baseline WBC (31% increase in risk for each 1×10^9/l drop). Risk is not dose-related (Munro *et al*, 1999).

Of patients treated with clozapine,x 0.7% develop agranulocytosis which is potentially fatal. Over 80% of cases develop within the first 18 weeks of treatment. Risk factors include increasing age and Asian race (Munro *et al*, 1999). Some patients may be genetically predisposed (Dettling *et al*, 2001). Although the time scale and individual risk factors for the development of agranulocytosis are different from those associated with neutropenia, it is impossible to be certain in any given patient that neutropenia is not a precursor to agranulocytosis.

Life cycle of neutrophils

Approximately 90% of white blood cells remain in storage in the bone marrow. The total lifespan of a neutrophil is 11–14 days, although once released into the circulation neutrophils die within hours. Infection stimulates release and can triple the WBC in a matter of hours. After being released from the bone marrow, neutrophils can either circulate freely in the bloodstream or be deposited next to vessel walls (margination) (Abramson & Melton, 2000). All of these neutrophils are available to fight infection. The proportion of marginated neutrophils is greater in people of African–Caribbean origin than in Caucasians, leading to a lower apparent WBC in the former.

Effect of lithium on the WBC

Lithium increases the neutrophil count and total WBC both acutely (Lapierre & Stewart, 1980) and chronically (Carmen *et al*, 1993). This 'side-effect' of lithium has been used successfully to raise the WBC during cancer chemotherapy (Greco & Brereton, 1977; Ridgeway *et al*, 1986; Johnke & Abernathy, 1991) and in patients treated with carbamazepine (Kramlinger & Post, 1990).

While it is widely known that lithium can cause neutrophilia, the magnitude of this effect is poorly quantified; primary literature is scarce. A mean neutrophil count of 11.9×10^9/l has been reported in patients treated with lithium (Lapierre & Stewart, 1980) and a mean rise in neutrophil count of 2×10^9/l in patients treated with clozapine after the addition of lithium (Small *et al*, 2003).

Neutrophilia does not seem to be clearly dose-related (Lapierre & Stewart, 1980; Carmen *et al*, 1993) although a minimum lithium serum level of 0.4 mmol/l may be required (Blier *et al*, 1998). The mechanism is not completely understood: direct stem cell stimulation (Kramlinger & Post, 1990), stimulation of granulocyte-macrophage colony-stimulating factor (GM-CSF; Ozdemir *et al*, 1994), stimulation of cytokines (Phiel & Klein, 2001) and demargination (Small *et al*, 2003) have all been suggested.

Case reports

Lithium has been used to increase the WBC in a patient whose baseline count was too low to allow initiation of treatment with clozapine (Boshes *et al*, 2001). It has also been used successfully in patients who have developed neutropenia with clozapine, thus allowing clozapine treatment to continue (Silverstone, 1998; Blier *et al*, 1998; Adityanjee, 1995). This approach has also been used successfully in children (Sporn *et al*, 2003). All patients had serum lithium levels > 0.6 mmol/l.

Treatment with lithium has also been reported to speed the recovery of the WBC when prescribed after the development of clozapine-induced agranulocytosis (Blier *et al*, 1998).

Other potential benefits of clozapine–lithium combinations

Combinations of clozapine and lithium may improve symptoms in schizoaffective patients (Small *et al*, 2003) and those with refractory bipolar illness (Suppes & Yang, 1994; Puri *et al*, 1995). There are no data pertaining to schizophrenia.

Potential risks

Lithium does not seem to protect against clozapine-induced agranulocytosis; one case of fatal agranulocytosis has occurred with this combination (Gerson *et al*, 1991) and a second case of agranulocytosis has been reported where the bone marrow was resistant to treatment with GM-CSF (Valevski *et al*, 1993).

Up to 20% of patients who receive clozapine–lithium combinations develop neurological symptoms typical of lithium toxicity despite lithium levels being maintained well within the therapeutic range (Small *et al*, 2003; Blake *et al*, 1992).

Patients who receive lithium are susceptible to all of the side-effects of lithium treatment and should be monitored in the usual way.

The use of lithium to increase the WBC in patients treated with clozapine constitutes off-label prescribing. The potential consequences for the prescriber are outlined in Box 1.

Box 1. Off-label prescribing

- The prescriber may be at increased risk of litigation if things go wrong
- He/she will be expected, by the courts, to have considered the risks and benefits of all treatment options, with due regard to the evidence available (Bolitho *v.* City and Hackney Health Authority, 1997)
- The actions taken should be supported by a respected body of professional opinion (Bolam *v.* Friern Hospital Management Committee, 1957)
- The prescriber's actions must be able to withstand logical analysis (Bolitho *v.* City and Hackney Health Authority, 1997)
- The prescriber may be criticised for not obtaining the patient's informed consent (or the specific consent of a second opinion doctor)

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Concluding comments

In summary, lithium may be useful in increasing the WBC in patients with low baseline counts who would benefit from treatment with clozapine or in those who develop neutropenia while treated with clozapine. A serum lithium level of >0.4 mmol/l may be required. Lithium does not protect against agranulocytosis. If the WBC continues to fall despite lithium treatment, consideration should be given to discontinuing clozapine. Particular vigilance is required in patients known to be at high risk of agranulocytosis, notably older adults and those of Asian origin, during the period of highest risk (the first 18 weeks of treatment).

Psychiatrists should be aware of the limited evidence that supports this prescribing practice and the potential outcome from litigation if things go wrong.

Declaration of interest

None.

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