Lithium and Clozapine Rechallenge: A Retrospective Case Analysis

Richard A. Kanaan, M.R.C.Psych.;
and Robert W. Kerwin, F.R.C.Psych., Ph.D.

Background: Clozapine is a uniquely effective antipsychotic, although its use is limited by the risk of neutropenia. Lithium is occasionally prescribed during a clozapine rechallenge, with the hope that it will prevent a second neutropenia or agranulocytosis. There are concerns, however, that lithium use will mask the onset of a neutropenia, leading to a more severe dyscrasia. The objective of this analysis was to determine the utility and safety of lithium coprescription in clozapine rechallenge.

Method: A retrospective case analysis was performed of all patients who had experienced a previous clozapine-induced blood dyscrasia and had a clozapine rechallenge with lithium coprescribed in a tertiary referral center between September 1998 and September 2003.

Results: Twenty-five patients met the study criteria; 1 patient (4%) had a second episode of neutropenia or agranulocytosis while undergoing the rechallenge. This rate was significantly lower ($p = .021$) than the national (U.K.) rate (21.2%). Although recurrent dyscrasias were not more common, or more severe, than those seen with rechallenge in general, our single case did show some evidence that the patient's neutropenia was masked by lithium use.

Conclusion: This study provides support for the utility of lithium in preventing neutropenias in rechallenge; extra vigilance may be required, however, to detect masked blood dyscrasias.

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Received Aug. 30, 2005; accepted Nov. 3, 2005. *From the Department of Psychological Medicine (Dr. Kanaan) and the Section of Clinical Pharmacology (Dr. Kerwin), King's College London, Institute of Psychiatry, London, United Kingdom.*

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Corresponding author and reprints: Richard A. Kanaan, M.R.C.Psych., Institute of Psychiatry, Department of Psychological Medicine, P062, Weston Education Centre, London SE5 9RS UK (e-mail: r.kanaan@iop.kcl.ac.uk).

Clozapine is a dibenzodiazepine antipsychotic that is uniquely effective in treatment-resistant psychosis.[1] Unfortunately, 2.9% of patients treated with clozapine experience a neutropenia (neutrophils $< 1.5 \times 10^9$/L), and 0.8% experience an agranulocytosis (neutrophils $< 0.5 \times 10^9$/L) (U.K. figures[2]). Consequently, weekly blood testing is compulsory for all patients who are prescribed clozapine in the United Kingdom, with the required frequency dropping to every 2 weeks after 18 weeks and to every 4 weeks after 1 year.

Until 2004, this testing was managed exclusively by Novartis' Clozaril Patient Monitoring Service (CPMS), using standardized criteria. Prior to December 2002, any blood test showing white blood cell count (WBC) $> 3.5 \times 10^9$/L and neutrophils $> 2.0 \times 10^9$/L was considered "green," allowing clozapine to be prescribed as usual; blood tests with WBC $3.0–3.5 \times 10^9$/L or neutrophils $1.5–2.0 \times 10^9$/L were considered "amber," requiring a repeat, satisfactory blood result before prescription could proceed; and blood tests showing WBC $< 3.0 \times 10^9$/L, neutrophils $< 1.5 \times 10^9$/L, or platelets $< 50 \times 10^9$/L were considered "red," necessitating immediate, indefinite cessation of clozapine administration.

After European harmonization in December 2002, the criteria for "red" results were modified to require confirmation of a low result on a second test and making the stopping of clozapine treatment for low platelets advisory rather than compulsory.[3] The modification also acknowledged benign ethnic neutropenia (a nonpathologic baseline neutropenia most commonly seen in the United Kingdom in African Caribbeans[4]) and allowed prescription at lower blood counts in such patients after hematologic review.

Patients with a "red" result are prohibited from further licensed clozapine prescription, but, because of the drug's unique efficacy, some clinicians have offered such patients a clozapine rechallenge on an off-label basis. As the risk of a second agranulocytosis is much higher in those who have previously had a "red" result (38%, using the post-2002 criteria[5]), various methods of militating against repeat blood dyscrasias have been tried, including granulocyte colony-stimulating factor[6] and lithium. Lithium causes a reversible leukocytosis, which may potentially antagonize any neutropenia. Treatment with lithium has

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typically been commenced before the clozapine rechallenge[7] or if there are signs of a downward drift in the neutrophil count.[8] However, there are concerns that lithium coadministration may mask an incipient neutropenia, leading to a precipitous, catastrophic agranulocytosis.[9] Evidence for the utility and safety of lithium administration during clozapine rechallenge exists only at the level of case reports.

The National Psychosis Unit at the Bethlem Royal Hospital, London, offers nationwide tertiary referral for U.K. patients with schizophrenia-spectrum disorders. Many of their patients have previously failed initial treatment with clozapine, and the unit has offered a variety of therapies for these treatment-resistant patients, including off-label clozapine rechallenges with lithium cotreatment. The unit has employed both of the above strategies—both lithium pretreatment and the later addition of lithium if neutrophil counts decline. This study reviews the safety and efficacy of lithium cotreatment in clozapine rechallenge in a naturalistic, retrospective case analysis of patients from the Bethlem Royal Hospital over a 5-year period. We hypothesized that lithium coadministration would significantly reduce the rate of recurrence of clozapine-induced blood dyscrasias in those with a history of "red" results induced by clozapine alone.

METHOD

Patient details for all admissions to the National Psychosis Unit and Special Care Unit wards at the Bethlem Royal Hospital from September 1998 to September 2003 were obtained from the hospital's computerized patient information system. This system provided names, dates of birth, and gender and ethnicity information. Cross-referenced lithium levels from all patients with matching names or dates of birth over the same period were obtained from the hospital pathology laboratory database. Any discrepancies or duplications were resolved through the patient information system, or the patient's notes where necessary. This list was submitted to CPMS, who determined which patients from the list had received clozapine and the names of their current psychiatrists. CPMS then sought written permission from these psychiatrists for the release of their patients' hematologic information to us. Where permission was obtained, the entire blood test history for each patient was sent to us for analysis. (Because of the way clozapine was monitored in the United Kingdom at the time, this would constitute a complete set of blood counts the patient had ever had while prescribed clozapine.)

The incidence of lifetime "red" results (defined as leukopenia of WBC $< 3.0 \times 10^9$/L, neutropenia $< 1.5 \times 10^9$/L, or thrombocytopenia of $< 50 \times 10^9$/L—the pre-2002 criteria) was determined from the hematologic data. The onset and duration of the lithium administration for each patient with a "red" result were determined from the dates of their lithium levels. Our study group of interest was those who had a previous "red" result on clozapine treatment (without lithium) who went on to have a subsequent clozapine rechallenge with lithium coadministration. When this could not be clearly determined from the raw data, or when patients appeared to have 2 or more "red" results, we retrieved the patient notes for confirmation. The observed rate of a second "red" result (using post-2002 criteria) was compared with population-level rates provided by CPMS. The study was approved by the South London & Maudsley NHS Trust Ethics Committee.

RESULTS

Twenty-five patients met our study criteria. There were 287 admissions to the 2 wards during the study period, of which 69 had lithium levels recorded. Of these, 62 patients were confirmed as being treated with clozapine. Two psychiatrists refused permission for disclosure of their patients' hematologic data. Thirty-five of the remaining 60 patients had at least 1 lifetime "red" result using the criteria of the time (WBC $< 3.0 \times 10^9$/L, neutrophils $< 1.5 \times 10^9$/L, or platelets $< 50 \times 10^9$/L). Twenty-five of these patients had a "red" result while taking clozapine without lithium before undergoing a clozapine rechallenge with lithium and constituted our study group. Their mean neutrophil nadir during their first "red" result was 1.47×10^9/L. Lithium treatment was started shortly before or simultaneously with clozapine treatment in 12 of the 25 patients and at various times after the clozapine rechallenge in the other 13 patients (median = 57 weeks).

Only 1 of the 25 patients ("Mr. A" hereafter) had a second "red" result while taking both lithium and clozapine, using the modified criteria (WBC $< 3.0 \times 10^9$/L or neutrophils $< 1.5 \times 10^9$/L, confirmed on 2 consecutive daily samples). One further patient went on to have a second "red" result 4 years after stopping lithium treatment and has been considered a successful rechallenge for the purposes of this study. Seventeen of the other 24 patients are still taking clozapine; none are still taking lithium. The details of Mr. A and his blood dyscrasias are shown in Table 1; summary details of the other 24 patients are given for comparison.

Case Report

Mr. A was a 26-year-old white man with a 7-year history of refractory schizophrenia marked by auditory, visual, and olfactory hallucinations and a history of polysubstance abuse. He had been treated with clozapine in 2000, but had developed an agranulocytosis after this was augmented with olanzapine, leading to a chest infection. He was transferred to the National Psychosis Unit in 2003. As the patient had developed the agranulocytosis in the period immediately following the augmentation of clozapine, it

Table 1. Characteristics of 1 Patient Who Did and 24 Patients Who Did Not Develop a Second Blood Dyscrasia While Taking Lithium and Clozapine

Characteristic	Patient With Second Blood Dyscrasia	Other Patients[a]
Age, y[b]	27	34
Gender	Male	N = 14 male N = 10 female
Ethnicity	White	N = 11 African Caribbean N = 6 White N = 1 Asian N = 6 unspecified
Duration of clozapine treatment, wk[c]	4	201
Duration of lithium treatment, wk[c]	10	168
Lithium dose, mean, mg	800	700
Lithium level, mean, mmol/L	0.41	0.54

[a]Data for age, treatment duration, and lithium dose are mean values.
[b]Age at final clozapine blood test.
[c]Duration of treatment from initiation until the earliest of the date of this study or the date of stopping clozapine treatment.

was felt that olanzapine, or the combination, might have been responsible. As he had subsequently shown a lack of clinical response to a variety of other antipsychotics, it was decided to rechallenge with clozapine, after pretreatment with lithium.

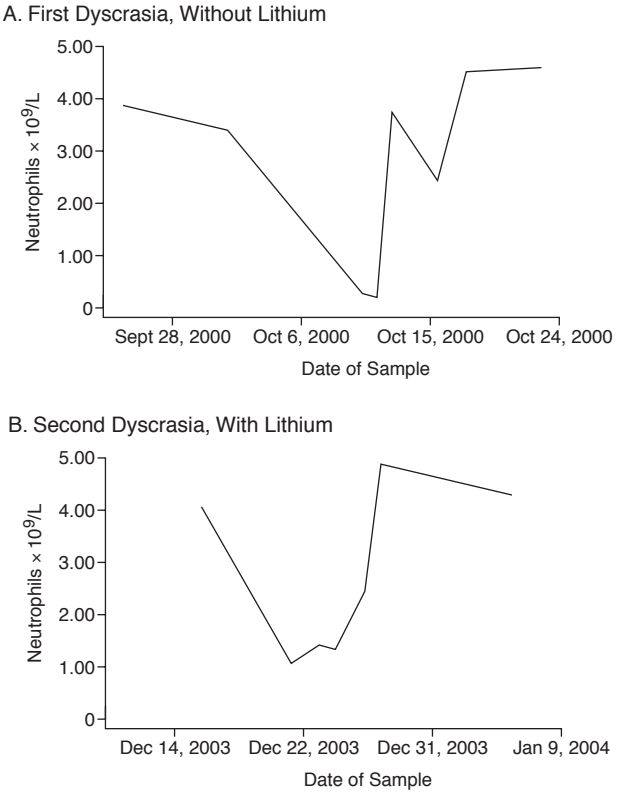
Lithium carbonate was started in September 2003 and titrated up to 800 mg per night. After a period of 6 weeks, clozapine was started and titrated upward as haloperidol and olanzapine were titrated down. Soon after the clozapine treatment was started, the patient developed a nonproductive cough, and a chest infection was diagnosed clinically, confirmed by chest x-ray, and treated empirically with amoxicillin. His blood count remained normal, and the patient appeared to respond to the antibiotics.

After 2 more weeks (1 month on clozapine treatment in total), the patient again became unwell, with pyrexia and hemoptysis. Blood tests revealed a neutropenia (1.03×10^9/L), which was confirmed on repeat testing, and the clozapine and lithium treatment was stopped. He was admitted to the local general hospital and treated with intravenous antibiotics for pneumonia. At the time of his neutropenia, in addition to clozapine 250 mg, Mr. A was taking lithium carbonate 800 mg per night, haloperidol 5 mg/day, diazepam 5 mg/day, amoxicillin 500 mg t.i.d., and procyclidine 5 mg/day. Neutrophil counts during Mr. A's 2 blood dyscrasias are shown in Figure 1. Mr. A fully recovered and is no longer taking lithium or clozapine.

Comparison With U.K. National Rate of Blood Dyscrasia in Clozapine Rechallenge

As CPMS were the sole prescriber during the period of our study, they have a complete sample of patients who were rechallenged in the United Kingdom. Nationally, over an equivalent 5-year period (December 1998 to December 2003), CPMS reports that 40 (21.2%) of 189 rechallenge patients had a second "red" result, using the criteria of our study (data from CPMS, April 2005). Our finding of a second "red" result in 1 (4%) of 25 patients is significantly lower than this figure (p = .021, cumulative 1-sided binomial probability), supporting our hypothesis that lithium is protective against blood dyscrasias in clozapine rechallenge.

Figure 1. Neutrophil Count Graphed Against Time in a Patient Who Developed 2 Blood Dyscrasias During Clozapine Treatment



DISCUSSION

The literature on rechallenge consists of case reports and case series. The largest of these was conducted by Novartis, looking at U.K. national data.[5] They found that 20 (38%) of 53 patients undergoing a rechallenge had a repeat blood dyscrasia and that in 17 (85%) of these cases, the second dyscrasia was more serious than the first. Although examination of a large cohort in the United Kingdom[2] found that increasing age, Asian ethnicity, and female gender predisposed to an initial dyscrasia with clozapine, these factors were not found to be significant in this much smaller rechallenge cohort.

There are several case reports and 1 randomized controlled trial of the safety and efficacy of lithium and cloza-

pine coprescription. Bender et al.[10] found the combination to be effective in 84% of their case series of 44, but found that 64% of patients had adverse events, including 8 with transient neurotoxic events. In a randomized controlled trial of lithium or placebo with clozapine, Small et al.[11] found no benefit with lithium and 2 neurotoxic events in 10 schizophrenic patients. There have also been reports of diabetic ketoacidosis,[12] neuroleptic malignant syndrome,[13] seizures,[14] and discontinuation organic psychosis,[15] in addition to blood dyscrasias.[9] There have also been concerns that lithium could make clozapine-induced blood dyscrasias more severe, or more dangerous, by masking their early stages.[9]

The literature on lithium coprescription during rechallenge is more sporadic, yielding only 7 cases in adults[7,8,16–18] and 2 in children.[19] All reported cases were successful. Our study adds considerably to this pool of data and is therefore potentially of considerable clinical significance. It offers the first systematic support for an intervention that may allow a group of severely ill patients to persist with the only antipsychotic that is of proven benefit to them: 24 of 25 patients tolerated lithium coprescription without developing blood dyscrasias, significantly lower than the national rate. The position is more complicated with regard to safety, however.

Certainly, with regard to the frequency of blood dyscrasias, lithium appears to be protective. In the case of Mr. A, his second dyscrasia was both briefer and less severe than his first (when he was not taking lithium; see Figure 1). However, the unusual presentation of a chest infection, in an otherwise healthy young man, while his blood count was still normal, might suggest that he was indeed in some way immunocompromised while still registering a normal blood count. To that extent, the lithium may have masked the hematologic evidence of the dyscrasia initially. Furthermore, his second dyscrasia developed more rapidly than his first—much more so, if we consider it to have been initially masked by the lithium. This appears to be a common feature of recurrent dyscrasias, however, irrespective of lithium use: in the national sample, a more rapid onset of the second dyscrasia was found in all but 3 cases (median = 5.5 weeks, compared with 81.5 weeks for the first dyscrasia).

Our study has several limitations. First, our study was naturalistic, and the sample may have been selected for the intervention on the basis of criteria that make it unrepresentative. For example, it is probable that a qualitative analysis of previous blood results was instrumental in screening out subjects who were thought likely to have a second dyscrasia (see Clinical Recommendations). In addition, age, Asian ethnicity, and female gender have all been found to increase the risk of agranulocytosis,[2,20] whereas our group was relatively young, mainly male, and only included 1 patient with Asian ethnicity. Second, our data acquisition method imposed limitations on our analysis. As we acquired most of our data without reference to the patient notes, we cannot, in most cases, confirm the motivation for lithium treatment, the precise dates of starting and stopping lithium treatment, the clozapine dose, the reasons for stopping lithium or clozapine treatment, and whether there were other risk factors for agranulocytosis present, such as valproate coprescription. It is also possible, although unlikely, that some other of the 287 patients admitted to the ward over this period were prescribed lithium, but never had their levels checked and were thus excluded from our study. Potentially, such subjects could have had immediate dyscrasias, before it made sense to check lithium levels, and thus our sample may have been biased.

The change in definition of "red" results also slightly complicated our analysis. We chose to define our first "red" result by the pre-2002 criteria and any recurrent "red" by the post-2002 criteria, as these reflected the clinical algorithms of their times and facilitated comparison with data available from the CPMS. The effect of the change in criteria was to make some results that were previously considered dangerous no longer grounds for stopping clozapine treatment. Therefore, in our study, some of the patients who initially had a "red" result, requiring rechallenge, would by today's criteria be allowed to continue taking clozapine without impediment. This is reflected in the different figures for national recurrence rates of rechallenge: 38% of patients who had a first "confirmed red" result (i.e., using the post-2002 criteria) went on to have a second "red" result on rechallenge,[5] but only 21% of those whose first "red" result was determined according to the pre-2002 criteria went on to have a second "confirmed red" result (data from CPMS, April 2005). Future studies utilizing a prospective design and fixed subject and dyscrasia criteria would further clarify the utility and safety of this intervention.

Clinical Recommendations

A clozapine rechallenge carries a clear risk to the patient and must be undertaken in a very careful manner. The most important factor to consider is patient selection. Although the precise basis of the neutrophilic effect of lithium is unknown, it is unlikely that it would protect against a "genuine" clozapine-induced neutropenia. Rechallenges with lithium are therefore only recommended when it is thought that there was an alternative cause for the previous neutropenia, such as benign ethnic neutropenia. There are no infallible proofs of the cause; however, certain guidelines may be useful. In cases in which the first dyscrasia occurred quickly (within the first 18 weeks), was severe (an agranulocytosis), or was prolonged (more than 2 days), a rechallenge would not be recommended, unless an explanation other than clozapine was strongly favored. A graph of the patient's previous dyscrasia can help to distinguish the precipitous (and

therefore more likely to be clozapine-induced) from the gentle decline and low baseline seen in benign ethnic neutropenia. In the United Kingdom, clozapine prescription is controlled by monitoring services, such as CPMS, and all prescription after a previous dyscrasia is strictly off-label. Furthermore, each of the clozapine monitoring services will impose its own checks on which patients may have rechallenges—typically on a similar basis to those outlined above.

If the decision to rechallenge with lithium has been made, the patient should be admitted to provide sufficiently close monitoring. Baseline tests, including electrolytes, thyroid function, and blood count, should be taken as with any clozapine challenge. Lithium treatment should be started and titrated upward to a plasma level of > 0.4 mmol/L[17] and continued for 1 to 2 weeks. If a repeat white cell count is within the normal range, clozapine treatment may be restarted, with at least weekly blood tests for the first 18 weeks, reducing the frequency thereafter as normally. Clearly, all staff should be alert for signs of possible infection, with regular clinical examination, and repeat blood tests if there are clinical suspicions.[21]

Drug names: amoxicillin (Trimox, Amoxil, and others), clozapine (Fazaclo, Clozaril, and others), diazepam (Diastat, Valium, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), procyclidine (Kemadrin).

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