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CAN WE PREVENT BLOOD DYSCRASIA (LEUCOPENIA, THROMBOCYTOPENIA) AND EPILEPTIC SEIZURES INDUCED BY CLOZAPINE

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SUMMARY

Clozapine is associated with various haematological adverse effects, including leukopenia, neutropenia, agarnulocytosis, leukocytosis, anaemia, eosinophilia, thrombocytopenia and thrombocythaemia. Recognition and treatment of clozapine-related seizures also will become increasingly important as clozapine use grows in the 1990s.

The decision to stop clozapine as a result of haematological adverse effects or seizures is a frustrating one for the clinician, and frequently disastrous for the patient. Cessation of treatment results in relapse. In case that patient is unresponsive to other antipsychotic, restarting clozapine should be consider, despite the risk involved. As the risk of a second agranulocytosis is much higher in those patients, various methods of militating against repeat blood dyscrasias have been treated, including granulocyte colony-stimulating factor and lithium. The decision to restart clozapine should be taken on case-by-case basis and should take into account the likely risks and benefits of restarting. Prior response to clozapine and magnitude of patient deterioration on stopping treatment are important factors to take into this consideration. Clozapine-related seizures did not preclude successful treatment with clozapine. A strategy that has been proposed to reduce the occurrence of seizures is the addition of an anticonvulsant agent.

However, clozapine does induce a variety of adverse effects, most of which are of limited duration and either preventable or manageable if a number of simple clinical procedures are followed. With careful haematologyc control, the risk of agranulocytosis can be minimized and in case of clozapine related seizures recommendations include dose reduction, electroencephalogram (EEG), plasma-level monitoring and prophylactic antiepileptic treatment. Re-exposure to clozapine may rarely be attempted where there are facilities for very close and frequent monitoring.

Key words: *clozapine - blood dyscrasia – leucopenia – thrombocytopenia - epileptic seizures*

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INTRODUCTION

Clozapine is an atypical antipsychotic agent with an established and valuable role in treatment-refractory schizophrenia (Taylor et al. 2000) Most schizophrenia guidelines now recommend that clozapine is prescribed after patients symptoms fail to respond to adequate trials with two antipsychotics (McEvoy 2006). Soon after it was first introduced into clinical use in Europe in the late 1960s and early 1970s, the haematological adverse profile of clozapine became apparent. In Finland in 1974, eight deaths resulted from agranulocytosis in patients taking clozapine. Clozapine remains the antipsychotic of choice for refractory schizophrenia despite its propensity for serious blood disorders **(**Whiskey 2007).

Clozapine is associated with other serious adverse effects such as thromboembolism (Hagg 2000), myocarditis, cardiomyophaty (Killian 1999), diabetes mellitus (Henderson 2000), weight gain (Taylor 2000) and seizures (Miller 2000). Less serious adverse effects include sedation, drowsiness, tahycardia, constipation and hyper salivation.

Clozapine induced blood dyscrasia

Clozapine is associated with various haematological adverse effects, including leukopenia, neutropenia, agarnulocytosis, leukocytosis, anaemia, eosinophilia, thrombocytopenia and thrombocythaemia (Miller 2000). The exact mehanism of clozapine induced haemathological disoreders is not known (Pirmohamed 1997) Agranulocytosis induced by clozapine is thought to be mediated either through a direct toxic effect or an immune-mediated reaction. It is also possible that both might co-exist or that several other different mechanisms might also be involved (Whiskey 2007).

Clozapine induced leucopenia

The cumulative incidence of agranulocytosis in patients treated with clozapine is approximately 0.8 % after 1 year. The period of greatest risk of haematlogical disorders with clozapine is during the first 18 weeks of treatment. Benign neutropenia occurs more frequently than agranulocytosis. Transient neutropenia, in which the neutrophil count drops below a defined value but returns to normal values with continued clozapine treatment,

occurs frequently. In sample of 68 patients receiving clozapine, transient neutropenia was found in 22% of the patients (Hummer 1994). Patients may also displayed a diurnal variation in the number of circulating neutrophils, such that a morning pseudo-neutropenia was normalised in the afternoon (Hummer 1994, Ahokas 1999).

Clozapine induced thrombocytopenia

Haematological disturbances resulting from clozapine include agranulocytosis, leucocytosis, eosinophilia and neutropenia (Hampson 2000) and rarely described low platelet count (Mihaljević-Peleš et al. 2001, Lambertenghi Deliliers et al. 2000).

Platelet dysfunction and thrombocythopenia rarely occur during clozapine therapy, but constitute an important source of morbidity and mortality if they are not detected and therapy is discontinued. The manufacturer recommends discontinuing clozapine when the platelet count falls below 100,000 /muL and resuming therapy when the count returns to within normal range (150,000 – 450,000/muL). If thrombocytopenia recurs, clozapine should be permanently discontinued (Gonzales et al. 2000).

Rudolf J at al. reported that neutropenia was successfully treated with G-CSF, but theombopenia persisted and resolved spontaneously after 14 days. Bone marrow toxicity of clozapine is not restricted to white cell maturation, but may also impair thrombocytopoesis (Rudolf et al. 1997). Leucocyte count monitoring is a mandatory clinical procedure during clozapine treatment. On the other hand, plated count monitoring is usually not recommended as a routine clinical procedure. Mihaljevic-Peleš at al. concludes that bone marrow toxicity from clozapine is not restricted to leucocyte maturation but may impair thrombocytopoiesis as well. To prevent serious clinical manifestation of bone marrow depression, routine monitoring of platet count could be a desirable procedure in patients treated with clozapine (Durst et al. 1993).

Clozapine induced seizures

Recognition and treatment of clozapine-related seizures will become increasingly important as clozapine use grows in the 1990s (Devinsky et al. 1991).

Much has been written on clozapine's propensity for lowering the seizure threshold (Devinsky 1994, Pacia 1994, Sajatovic 1996, Silvestri et al. 1998, Welch et al. 1994), including guidance for the management and prophylaxis of clozapine-related seizures (Devinsky 1994, Taner et al. 1998, Welch et al. 1994). Devinsky at al. found that 2.8% of patients had generalized tonic-clonic seizures during treatment with clozapine. Clozapine-releated seizures appear to be dose-related. High-dose therapy (grater then or equal to 600 mg/day) was associated with grater risk of seizures (4.4%) than medium (300 to 600 mg/day; 2.7%) or low doses (less than 300 mg/day; 1.0%). Also, rapid upward titration may increase seizure risk. Patients may continue on clozapine treatment with reduction of dose or addition of an antiepileptic medication (Devinsky 1994).The risk of seizure during clozapine treatment has been estimated at approximately 1% to 4.4% dependent on dose (Devinsky et al. 1991, Devinsky et al. 1994). However, seizures have been observed at all stages of treatment (Sajatovic 1996), at both high and low doses, and thus may not in fact be dose-dependent (Pacia 1994). They are perhaps more likely to be blood-level related (Greenwood-Smith et al. 2003) than dose-related and therefore more useful measures in assessing the risk of seizure may include EEG and plasma blood-level monitoring.

Restarting clozapine after blood dyscrasia and seizures

The decision to stop clozapine as a result of haematological adverse effects or seizures is a frustrating one for the clinician, and frequently disastrous for the patient.

Cessation of treatment results in relapse. In case that patient is unresponsive to other antipsychotic, restarting clozapine should be consider, despite the risk involved (Whiskey 2007).

Patients with a result in WBC blood tests showing < 3.0 x 10 9/L 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 a off-label basis. As the risk of a second agranulocytosis is much higher in those patients, various methods of militating against repeat blood dyscrasias have been treated, including granulocyte comlony-stimulating factor (Hagg 2003) and lithium. Lithium causes a reversible leukocytosis, which may potentially antagonize any neutropenia. However, there are concerns that lithium co-administration may mask an incipient neutropenia, leading to catastrophic agranulocytosis (Valevski 1993).

It has been recognised that lithium treatment causes an increase in WBC counts in almost al haematologically normal patients who have been prescribed lithium for between 1 and 4 weeks. There is no correlation between increases in WBC counts and lithium dose or serum concentrations, age, gender or bodyweight (Papadaki 2002, Stein 1978), although lithium concentrations of at least 0,4 mmol/ L may be required. The usual magnitude of elevation of the WBC count is approximately 2.0 x 10 9/L, or between 30% and 45% greater than pre-treatment levels (Papadaki 2002, Small 2003). Lithium treatment should be started and titrated upward to a plasma level of > 0.4 mmol/L (Blier 1998) and continued for 1 to 2 weeks. If a repeated white cell count is within the normal range, clozapine treatment may be restarted, with et least weekly blood tests for the first 18 weeks (Kanaan 2006). In the largest and most recent series reported (a retrospective chart review of 25 patients undergoing clozapine rechallenge using lithium pre-treatment) there was only one case of a second episode of neutropenia (Kanaan 2006).

The combined pharmacotherapy of clozapine and lithium is still a controversial issue although the evidence base for this controversy remains week. Binder et al. reviewed medical records of 44 patients who had been treated with combination of clozapine and lithium over 3 years. For 37 patients (84%) the combined treatment was rated effective. In 28 patients (64%) et least one adverse event was documented including 8 with transient neurotoxic events. The majority of adverse events that have been documented had also been reported with clozapine monotherapy et similar rates. Their data do not indicate an increased risk for epileptic seizures under the clozapine-lithium combination therapy (Bender 2004). Combining clozapine with lithium tretmant should be conducted under strict clinical guidelines and by avoiding additional co-medication with serotoninergic drugs or other susbstance that interfere with clozapine metabolism and body clearance. Serotoninergic antidepressants as a co-medication may increase clozapine plasma levels and therefore the risk of neurological adverse events – trough CYP1A2 inhibition as clozapine is mainly metabolized via cytochrome P4501A2 (CYP1A2) (Bertillson 1994). The use of a lithium-clozapine combination is not without risk. There is a concern that the use of lithium may mask impending agranulocytosis (Kramlinger 1990). Close monitoring of the patients is essential because it is rarely possible to completely rule out the contribution of clozapine to the blood dyscrasia and because lithium does not protect against clozapine-related agranulocytosis.

Despite seizures are a well-documented risk of therapy with clozapine, several anticonvulsants, including valproic acid, phenytoin and carbamazepine, have been shown to be helpful in the prevention or/and treatment of these seizures (Usiskin et al. 2000, Devinsky et al. 1994). Despite the known risks, many clinicians involved in the care of those prescribed clozapine do not take steps to prevent seizure or to adequately measure or monitor its risk. When considering the adverse affect profile of clozapine, much emphasis is placed on the drug's ability to cause blood dyscrasias and little on the risk of seizure (Sparshatt et al. 2008). The decision to restart clozapine should be taken on case-by-case basis and should take into account the likely risks and benefits of restarting. Prior response to clozapine and magnitude of patient deterioration on stopping treatment are important factors to take into this consideration.

We report the case of 34-year old female patient with refractory schizophrenia who had previously been treated with clozapine and developed leucopoenia, thrombocytopenia and epileptic seizures by dose of 400 mg of clozapine. Plated count was 133 x 10 9/L and leukocyte count was 2,8 x 10 9/L. Because of that clozapine treatment was suspended. After rechallange of clozapine combined with lithium and metilphenobarbitone the platet count reached the lowest value 21 x 10 9/L and the leukocyte count reached the lowest value 21 x 10 9/L and there was no epileptic seizures on the dose of 400 mg of clozapine. She was discharged while receiving 400 mg/day of clozapine, 900 mg/day of lithium, and 200 mg/day of methilphenobarbitone. After 3 months of that therapy, the patient showed significant improvement, and there was no evidence of recurrent blood dyscrasia or seizure. Lithium and methilphenobarbitone should be considered for the treatment of clozapine-induced leucopenia and seizures as a prophylaxis for patients taking clozapine who are at increased risk for that adverse event, especially patients with good previous clinical response to clozapine.

CONCLUSION

For many patients clozapine offers new hope for the successful pharmacological management of a disabling mental disorder. However, up to 17 percent of patients must discontinue treatment with clozapine because of adverse effects, which also

limit the rate at which the dose can be increased and the maximum dose that can be tolerated (Young et al. 1998). However, clozapine does induce a variety of adverse effects, most of which are of limited duration and either preventable or manageable if a number of simple clinical procedures are followed. With careful hematologic control, the risk of agranulocytosis can be minimized (Naber 1999). In cases of clozapine-induced neutropenia rechallenge may also be considered and lithium co-therapy may be required. Re-exsposure to clozapine may rarely be attempted where there are facilities for very close and frequent monitoring (Whiskey et al. 2007). Seizures associated with clozapine treatment occur at a rate of about three percent. Factors which seem to increase the likelihood of seizures include high dose of clozapine, rapid dose titration, the concurrent use of other epileptogenic agents and a previous history of neurological abnormalities. Clozapine-related seizures did not preclude successful treatment with clozapine (Wilson et al. 1994). A strategy that has been proposed to reduce the occurrence of seizures is the addition of an anticonvulsant agent (Toth et al. 1994). Recommendations include dose reduction, electroencephalogram (EEG), plasma-level monitoring and prophylactic antiepileptic treatment.

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