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CLOZAPINE-INDUCED AGRANULOCYTOSIS AND USE OF G-CSF

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ABSTRACT

Use of clozapine is attended with the serious though rare risk of agranulocytosis. Clozapine-induced agranulocytosis is reversible with the use of cytokines like granulocyte-colony stimulating factor (G-CSF). Reports of the haematological complication of clozapine have not been forthcoming from India though it has been in use for nearly three years. This report is on an young patient who developed total absence of granulocytes during the 4th month of treatment who was successfully treated with G-CSF.

Key Words : Clozapine, agranulocytosis, G-CSF

Clozapine is used in the treatment of schizophrenic patients refractory or intolerant to conventional neuroleptics. Its use is limited due to the potential risk of producing agranulocytosis. The cumulative incidence of agranulocytosis is 0.80% after 1 year and 0.91% after 1½ years, maximum during the first 3 months of treatment, in women and the elderly (Alvir & Lieberman, 1994). The agranulocytosis due to clozapine is reversible but can be fatal in 0.03% of patients who develop the complication (Atkin et al., 1996). Cytokines, namely granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) have been used to shorten the course of agranulocytosis and should be considered in patients with profound neutropenia (Chin Yee et al., 1996). Clozapine had been introduced in India for nearly three years and is understood to be extensively used. However no clinical reports of agranulocytosis have been reported in psychiatric literature whereas it has often been reported from the west where the monitoring protocol is as strictly followed, if not more.

This paper reports an young boy who developed total agranulocytosis with clozapine and was successfully treated with G-CSF.

CASE REPORT

Mr. P, a 13 year old boy hailing from a village about 100 kms from Chennai was diagnosed as suffering from schizophrenia in October 1996 with symptoms of aggressive behaviour, refusal to go to school, talking incoherently with a lisp, poor self care, poor concentration, insomnia, hallucinatory behaviour and wandering tendency for the 2 months preceding consultation with a psychiatrist. Neurological evaluation including a CAT scan and EEG did not reveal any coarse brain disease. At the time of consultation with the author (TNS) he was receiving treatment with haloperidol and chlorpromazine. The boy was then seen to be drowsy and having parkinsonian symptoms. Excepting for insomnia and aggressive behaviour there had not been much change in his psychiatric picture. He was started on trifluoperazine and low dose benzodiazepines which helped reduce the drowsiness and parkinsonian symptoms but no further change in the overall

behaviour. Clozapine was then started in doses of 50 mg/day and increased to 125 mg/day in a month. At the end of 12 weeks, the patient had remitted from all the symptoms of the illness and was showing keen interest in studies and was allowed to rejoin school at his village. The need for close monitoring of the blood counts was impressed upon the parents who were also told that if the boy developed any fever or general ill health they should immediately report to the consultant, as the drug might need to be stopped.

Three weeks later the boy was admitted to the hospital with fever and sore throat which had started 10 days earlier. They had consulted the physician near home who advised some oral antibiotics and advised them to continue clozapine. When the boy became moribund they brought him to the consultant. At admission the patient was febrile and dehydrated. He had diarrhoea and oral thrush. Skiagram of the chest revealed patchy pneumonia. Blood hemogram revealed a total leukocyte count (TLC) of 1000/cmm with no neutrophils (Absolute neutrophil count (ANC=O). Blood culture grew pseudomonas organisms. Bone marrow examination showed severe depletion of myeloid precursors (Promyelocyte =0 5%, Myeloblast =2.5%)

TABLE 1
TOTAL LEUCOCYTE AND ABSOLUTE NEUTROPHIL COUNTS

Time of examination	Leucocyte count /cmm	Neutrophil count /omm
Before clozapine	5900	2537
4 weeks of clozapine	5900	2301
12 weeks of clozapine	5400	2430
At admission to hospital	1000	Nil
G-CSF given - day 1	1200	Nil
Day 3	2210	Nil
Day 5	3200	288
Day 8	8800	1908
Day 10	30100	18361
Day 24	15900	11178
Day 60	11,100	7500

The boy was kept in reverse isolation and started on systemic broad-spectrum antibiotics and antifungal agents. Granulocyte-Colony Stimulating Factor (G-CSF) was started on the 2nd day after admission and given subcutaneously for five days at a dose of 150 micrograms per day. Granulocytes started appearing in the peripheral blood on the 5th day after starting G-CSF. The counts normalised in the next 3 days and overshot the normal in 7 days. The cell counts done serially is given in table 1. The systemic infections cleared within 5 days after the granulocytes returned and the boy was discharged after 10 days. At discharge he was started on risperidone. After 2 months follow-up the boy was in remission from active symptoms and was attending the school though he tended to exhibit some negative symptoms. His leucoctye and neutrophil counts were normal.

DISCUSSION

The literature on clozapine-induced agraulocytosis (Gerson, 1994) had not reported the extreme degree of the condition as in this patient who had total absence of granulocytes in the peripheral blood corroborated by severe depletion of granulocyte precursor cells in the bone marrow. This total agranulocytosis probably occurred due to the delay between the time the boy developed neutropenia manifesting as fever and sore throat and the time of hospitalisation, during which time he was unfortunately continued on the drug. Reports of such a complication in children and adolescents had not featured in the literature available to the authors. Clozapine was used for the boy not only because he was intolerant and non-responsive to other drugs but also taking into reckoning its beneficial effect on the cognitive function as well as low risk for tardive dyskinesia (TD) and other extrapyramidal symptoms (Meltzer, 1992). It had been observed that patients of schizophrenia with early onset respond

partially to conventional antipsychotic treatment and are at higher risk for developing TD (Gordon et al., 1994; Mozes et al . 1994)

The importance of close monitoring of the granulocyte count is highlighted by the report. It could be argued that the boy should not have returned to the home town where the monitoring was not followed properly. After being given clozapine the boy had shown significant improvement enabling him to rejoin school. Under such circumstances denying the boy that opportunity by making him stay in the city is defeating the very purpose of using the drug. If only the parents followed the instruction more strictly and their local physician was aware of the complication of clozapine and acted accordingly the severe complication could have been minimised. If use of clozapine is restricted to only the urban patients within easy reach of experts, then the schizophrenic patients, majority of who live in other areas, will be denied the benefits due to the drug, which is obviously not a good policy.

All medical practitioners should be aware of serious adverse effects like agranulocytosis due to drugs and should be able to atleast monitor patients who were put on the drug by the specialist. The concerned specialist and the pharmaceuticals have a responsibility in bringing this awareness, especially when new drugs are introduced. Otherwise adverse opinion will build up against the use of the drug as had happened to clozapine when it was first introduced in the 70's.

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