Case Report

DELAYED ONSET OF CLOZAPINE INDUCED AGRANULOCYTOSIS

PhineyTreesa Philip[1*], Aditya Senan[1], Sumi Reji[1]

Pharm D, Nandha College Of Pharmacy, Erode, India.

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ABSTRACT:

One of the most common adverse effects in the usage of clozapine in psychiatric setting is agranulocytosis and neutropenia which is idiosyncratic and the mechanism is unknown.Clozapine may be used in the treatment of chronic schizophrenia who fails to show an adequate response to standard antipsychotic drug treatment. It can also be used to reduce the risk of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of re-experiencing suicidal behaviour.Agranulocytosis will be at increased risk after two to three months of therapy.In this report we describe a case of clozapine-induced agranulocytosis treated by withdrawal of the causative drug and continuing the treatment with Quetiapine another potent atypical antipsychotic drug.

KEYWORDS:
Agranulocytosis, Clozapine, Schizophrenia

Corresponding author: PhineyTreesa Philip
E-mail: itsmephiney@gmail.com
Phone: +91-7845184401

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INTRODUCTION:

Clozapine is an atypical neuroleptic agent from the dibenzodiazepine group that has shown efficacy in schizophrenic patients refractory to other neuroleptic drugs. It has been impressive in both resolving the symptoms and improving in the quality of life [1]. Unlike classic neuroleptic agents, clozapine did not cause dystonia, Parkinsonism, tardive dyskinesia nor elevate prolactin levels[2]. It can provide relief from both positive and negative symptoms in patients with schizophrenia. Clozapine is also regarded as an "anti-manic agent" since it remains the most effective drug in patients with affective psychotic mania, whom fail to respond to adequate trials with two antipsychotics [3].

The term agranulocytosis was first used by Schultz in 1922, in patients with severe sore throat, extreme reduction or even total disappearance of granulocytes from the peripheral blood and in quick succession, sepsis and death [4]. Clozapine is known to produce agranulocytosis in about 1% of patients, which in certain cases limit its use in the treatment of psychiatric disorders [4]. This incidence rate is unequally higher than the estimated rates of drug-induced agranulocytosis in general, with few cases per million population per year and agranulocytosis induced by classical antipsychotics, with an incidence rate below 0.1% [4] [5] [6].Clozapine is thought to be the most effective atypical antipsychotic agent in patients with treatment-resistant schizophrenia and has shown a threefold overall reduction of risk of suicidal behaviours of schizophrenic patients [4]. The pathogenesis of clozapine-induced agranulocytosis is unknown, whether immunological, toxic or genetic mechanisms or a multistep phenomenon are responsible for such a life-threatening side effect [7]. The delayed onset of developing agranulocytosis after initial exposure of clozapine, which lasts at least 6–10 weeks, seems to be a strong argument against simple antibody or toxic mechanisms[8] [9].

In addition to the risk of life-threatening agranulocytosis, clozapine can also cause hypotension, seizures, tachycardia, sialorrhea, weight gain, and many other significant adverse effects. Adverse effects can limit the rate, at which the dose can be increased, as well as the maximum dose that can be tolerated by some patients[10].The risk of agranulocytosis is highest during the first 3 months of treatment with clozapine, and about 95 percent of the cases occur within 6 months of initiation of treatment[11].Datas suggest that 0.8 percent of patients receiving clozapine develop agranulocytosis within a year[2]. This is approximately 10 times the risk found with phenothiazines[10] [12]. Clozapine-induced agranulocytosis is commonly characterized by a gradual decrease in white blood cell (WBC) counts that occurs over several weeks[11].Although this hematologic condition is usually reversible within 14–22 days after discontinuation of clozapine therapy, patients with agranulocytosis remain at risk of infections for up to 4 weeks[13]. Patients who have experienced clozapine-induced agranulocytosis should not be rechallenged with the drug because of an increased mortality risk[11].

CASE REPORT:

A 54-year-old male with an 8-year history of undifferentiated chronic schizophrenia who had complaints had been treatedwith T.Clozapine 100mg BD along withT. Trifluoperazine 5mg,T.Aripiriprazole 10 mg.

He was admitted in the rehabilitation ward for the past 8 years with the complaints of hallucinations, delusions and disorganization. His blood counts were checked periodically and were found to be normal. Systemically he was fine. On mental state examination he was attractive, healthy and serious. He had suicidal tendency and had attempted thrice. Approximately 7 months after the initiation of clozapine, he became neutropenic: is WBC has fallen to $2x10^9$/L (4-$11x10^9$/L); his ANC was $0.25x10^9$/L (1.5–8x 10^9/L) as indicated in Table 1. He developed a dry cough, fever and chills.Clozapine was discontinued immediately. Systems review and examinations revealed no obvious focus for infections. Blood, urine, and sputum cultures were all negative. He was treated with intravenous ciprofloxacin 200mg iv bd, and his fever resolved in 24 hours. He was switched to oral ciprofloxacin 3 days later. Quetiapine 150 mg bd was introduced to the patient from the next day and a rise in ANC and WBC was observed within a week and eventually led to the patient recovery.

Table 1:

Laboratory investigations:

	WBC (white blood cells)	ANC (absolute neutropenic count)
Date of reaction	$2x10^9$/L	$0.25x10^9$/L
First week after withdrawal	$2.5\ x10^9$/L	$0.50x10^9$/L
Day 12	$5\ x10^9$/L	$2.5x10^9$/L

DISCUSSION:

Idiosyncratic drug-induced agranulocytosis (DIAG) is an adverse reaction to drugs due to abnormal susceptibility, peculiar to the individual whoresults in a severe reduction of granulocytes in the peripheral blood .The disorder may be life-threatening[3]. We describe a case of clozapine induced agranulocytosis which was managed by discontinuing the drug and adding Quetiapine to the treatment, where the patient responded positively to the therapy and an initial rise of the WBC and ANC was observed within a week.

Clozapine is thought to induce agranulocytosis through animmune-mediated mechanism. The drug appears to trigger the development ofantibodies against human leukocyte antigens (HLA) on bonemarrow progenitor cells with sparing of the stem cell compartment [1]. For patients with severe neutropenia, we recommend that a bone marrow aspiration be performed to rule out other causes of bone marrow failure [1].
A gradual, progressive decline in WBC or ANC should alert clinicians to the possible early development of agranulocytosis. Other markers in the blood count may include a rapid fall in neutrophils (even if WBC>3500/mm^3), eosinophilia, or the presence of immature myeloid forms [14].

In a Finnish study, Eosinophilia was observed to precede the development of agranulocytosis[15], but it has not been a consistent marker for this complication[16]. Should eosinophilia occur in association with leukopenia, dermatologic symptoms, or fever, discontinuation of clozapine is recommended[17]. In all cases of neutropenia, any medications that can potentially develop agranulocytosis should be discontinued immediately. For patients with mild neutropenia (ANC >1.5 × 109/L), the risk of infection is low[18] [19]. These patients should have their granulocyte count monitored until recovery. For patients with moderate levels of neutropenia (ANC 0.5 × 109/L to 1.5 × 109/L), more frequent monitoring for the development of infection and neutrophil recovery is recommended. Reverse isolation precautions are recommended by certain studies when the ANC is less than 0.5 × 109/L, although arguments exist about the actual benefits and efficacy of this approach[20] [21]. Any neutropenic patient who develops a fever should promptly be initiated with empiric broad-spectrum antibiotics, which are generally continued until neutropenia and signs of infection resolve.

In this case report the patient was identified with delayed onset of clozapine induced mild granulocytosis where the patient developed with dry cough and fever associated with chills was managed by intravenous antibiotic like ciprofloxacin and was changed to oral ciprofloxacin after 3 days. The fever resolved and the causative drug clozapine 100mg was changed to Quetiapine 150mg bd.

CONCLUSION:

The management of clozapine induced agranulocytosis is a significant challenge to the health care professionals as agranulocytosis is a life threatening condition. In all cases of agranulocytosis the potent drug should be withdrawn and granulocyte count should be monitored regularly. This study shows the incidence and management of clozapine induced agranulocytosis.

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