MARKED THROMBOCYTE COUNT VARIATIONS WITHOUT AGRANULOCYTOSIS DUE TO CLOZAPINE

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ABSTRACT

We report here a serendipitous observation of marked variations in blood thrombocyte count without agranulocytosis in a patient being treated with clozapine. Possible mechanisms of this thrombocytopenia and thrombocytosis related to clozapine are discussed, raising questions regarding monitoring of platelet counts along with granulocyte counts to prevent serious complications as a result of thrombocytosis or thrombocytopenia.

Key words: Clozapine, platelet, thrombocytopenia, thrombocytosis, adverse drug reaction

Clozapine, is an effective antipsychotic drug having potential benefit in patients refractory to the typical antipsychotic drugs (Kane et al., 1988). But its usage had been limited by its potentially life threatening side effects like granulocytopenia. Intensive precautionary monitoring of white blood cell total and differential counts at regular intervals have been introduced. However, platelet counts in patients receiving clozapine are not monitored. We herein report a case with marked variations in platelet counts while on treatment with clozapine.

CASE REPORT

Mr. A, age 19 years, single, student presented in December 1993 to National Institute of Mental Health and Neurosciences, Bangalore, with a 15 month history of social withdrawal, decreased personal care, disturbances in sleep and appetite and a history suggestive of catatonic symptoms. He had a past history of measles at the age of 5 years. Psychiatric examination revealed catatonic signs in the form of mutism and active negativism, lasting a week. Subsequently, delusions of reference and persecution, and first rank symptoms were elicited. A diagnosis of Paranoid Schizophrenia was made according to the International Classification of Diseases-10 (ICD-10, World Health Organisation, 1990). He was treated with trifluoperazine (20 mg/day) and had good clinical improvement for a year and half when he discontinued medication and had a relapse. On restarting trifluoperazine (20 mg/day), patient developed severe EPS and did not show improvement in his psychiatric
symptoms for 8 weeks. Patient was then started on clozapine (25 mg/day). Baseline haemogram, White Blood Cell Total Count (TC) and Differential Count (DC) were within normal limits. The dose of clozapine was gradually increased to 200 mg/day over a period of one month when the weekly haemogram remained within normal limits. Observations are available up to 38 weeks of treatment with clozapine. Total leucocyte count remained within normal limits of 5000 to 10,400 cells/cumm throughout, although fluctuations were observed, as shown in the graph (Fig. 1).

The patient's father inadvertently got platelet counts done. Platelet count showed marked variation. There was a gradual decrease from 16th week onwards reaching 45,450 cells/cumm (normal range 1.5-4 lakh/cumm.) by 24th week. Clozapine was stopped for a week and then restarted. By week 26, thrombocytosis with a count of 7,07,000 cells/cumm was noted. Patient had no evidence of inflammation, bleeding purpura, petechiae, tumour or iron deficiency. Platelet counts dipped to 1,00,000/cumm by weeks 28 to 30 which again rose to 6,56,500/cumm by week 36 on clozapine 150 mg/day. Bleeding time (1'50") Clotting time (5'45") and Prothrombin time (20", control 15") were within normal limits. There was no evidence of bleeding or thrombosis. However, the patient showed remarkable clinical improvement on clozapine 200 mg/day which has continued to date (37.5 mg/day). No further fluctuations have been noticed in the platelet counts since the last 15 months. The figure 1 gives a graphic representation of the platelet and white cell counts during the 38 weeks of treatment on clozapine.

DISCUSSION

In this case, monitoring of platelet counts was initially not advised, but was being done incidentally by the laboratory. On noticing the reduction in platelet counts for the first time, we advised the patient to have the platelet counts monitored regularly. Observations indicate that: (i) thrombocytopenia has occurred at doses of 200 mg/day which has ceased on either stopping the drug or reducing the dose to 150 mg/day; (ii) Thrombocytopenia was followed by thrombocytosis on the two occasions; (iii) There was no relationship between variations in platelet count and leucocyte count.

Regarding the possible mechanism of this observation, the first issue is whether the varying platelet counts are dose related. The significant change in platelet count was seen even with variation of clozapine dose by 50 mg/day. Hence it is difficult to conclude whether thrombocytopenia is dose related. Secondly, drug induced thrombocytopenia may occur either due to direct toxic effect of the drug on the marrow as an idiosyncratic reaction or due to a hypersensitivity reaction leading to excess destruction. The destruction of platelets stimulates production of platelets (Penington, 1984). This may explain thrombocytosis following thrombocytopenia on the two occasions. On the other hand, thrombocytosis may also be due to the direct effect of clozapine on the marrow. Thirdly, as shown in the graph (figure 1), total leucocyte count remained within normal limits. There does not seem to be a correlation between the variation in platelet counts and total leucocyte count. This raises the question whether the factors causing neutropenia/agranulocytosis and thrombocytosis are similar or different.

Focusing onto the consequences of thrombocytosis/thrombocytopenia, the effects may be benign as in this case or potentially lethal. Thrombocytopenia with a platelet count between 50,000 to 1,00,000/cumm causes mild prolongation of bleeding time. Platelet counts below 50,000/cumm. manifest with skin purpura on minor trauma and bleeding in the mucous membrane after surgery. Spontaneous bleeding, petechiae, ecchymoses, and hematomas occur when platelet counts drop below 20,000/cumm and can be fatal. Menorrhagia is a serious problem in women with thrombocytopenia. Thrombocytosis may be benign when it is secondary to cell destruction. However thrombocytosis may also lead to
either severe bleeding or thrombosis, which may be fatal (Penington, 1984). In a case report, clozapine related thrombocytopenia resulted in epistaxis (Durst et al., 1993).

The reviews on haematological side effects of clozapine are silent about platelet counts. There was just a single mention of thrombocytopenia. A review of database from the CPMS (Clozaril Patient Monitoring Service) of UK and Ireland showed that 4.3% of patients had to stop clozapine due to haematological reasons. Of 6316 patients, there were 182 cases of neutropenia, 48 of agranulocytosis, 38 of leucopenia and 6 of thrombocytopenia (Atkin et al., 1996). The authors have not discussed whether the thrombocytopenia occurred in those with other haematological abnormalities or the consequences of the same.

Our case raises the question about the need to monitor platelet count regularly during treatment with clozapine. There is a need for research to answer several questions in this regard. What is the incidence of thrombocytopenia/thrombocytosis? What is the mechanism by which clozapine causes this adverse effect? What is its relationship to neutropenia/agranulocytosis? Is the platelet variation due to clozapine benign/lethal? How long and at what intervals is monitoring of platelet counts necessary? Nevertheless, this report draws attention towards the significance of platelet counts in patients receiving clozapine.

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