CASE REPORTS

G-CSF Plasma Levels in Clozapine-Induced Neutropenia

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Background: Clinical reports emphasize the therapeutic usefulness of granulocyte colony-stimulating factor (G-CSF) in clozapine-induced granulocytopenia. Only sparse information exists, however, on the natural course of endogenous G-CSF plasma levels in this condition.

Methods: We monitored G-CSF and white blood cell (WBC) counts in a 73-year-old patient who developed granulocytopenia while being treated with clozapine for schizoaffective disorder. Clozapine treatment was discontinued immediately, and G-CSF serum levels were determined repeatedly during the clinical course.

Results: Whereas WBC counts increased again within 6 days after discontinuation of clozapine, G-CSF level decreased significantly within the same period. The rapid decrease of endogenous G-CSF levels paralleled by a normalization of neutrophil count was interpreted as the result of an intact regulatory mechanism of granulopoiesis. Therefore G-CSF therapy was not initiated. Owing to lack of therapeutic alternatives, it was decided to reintroduce clozapine. G-CSF levels decreased further, accompanied by an increase of WBCs, indicating stable bone marrow functioning.

Conclusions: Based on this observation, we assume that the course of G-CSF and WBC counts indicated an abortive form of toxic bone marrow damage with subsequent recovery. We conclude that monitoring of G-CSF levels may serve as a useful tool in the follow-up of patients in whom clozapine-induced bone marrow damage is suspected. Biol Psychiatry 2000;48:1113–1115 © 2000 Society of Biological Psychiatry

Key Words: Clozapine, neutropenia, granulocyte colony-stimulating factor, granulocytopenia

Introduction

Clozapine is an atypical neuroleptic agent with marked antipsychotic effects even in otherwise treatment-resistant psychoses. The clinical use of clozapine is limited by potential side effects, in particular because of the excessive risk of agranulocytosis (0.80% at 1, 0.91% at 2 years; Alvir et al 1993). After initiation of clozapine therapy a peak in the number of neutrophils is considered as an indicator associated with an elevated risk of subsequent granulocytopenia (Alvir et al 1995). It has been suggested that this early peak may refer to a release of granulocytes from endothelial cells, indicating an autoimmune process with subsequent bone marrow damage. There are only a few reports that emphasize the potential efficacy of granulocyte colony-stimulating factor (G-CSF) as a treatment in cases where clozapine therapy induced severe granulocytopenia (Gerson et al 1992; Gruner et al 1994). Application of G-CSF is limited, owing to its high costs and to potential side effects (i.e., allergic reactions or thrombocytopenia). Because the natural course of endogenous G-CSF plasma levels induced by granulocytopenia during clozapine treatment was up to now not described, we report on the following case.

Case Report

A 73-year-old female Caucasian patient developed neutropenia after 4 years of uneventful clozapine treatment (100 mg/day) for schizoaffective disorder. An idiopathic Parkinson’s disease was diagnosed 3 years ago and treated with the antimuscarine drug metixen (15 mg/b.i.d.) and L-dopa (187.5 mg/day). White blood cell (WBC) count was measured at regular intervals and revealed leukocyte levels ranging from 5.4 to 9.9/nL. The patient’s human leukocyte antigen haplotype did not correspond to that which has been reported to be associated with higher incidence of clozapine-induced agranulocytosis (Lieberman et al 1990). The patient was admitted because the WBC count had dropped to a granulocyte level of 2.5/nL (neutrophils: 34%) with no clinical signs of febrile infection. On admission, clozapine treatment was discontinued immediately. Subsequent control of WBC count revealed a slight increase to 3.1/nL (neutrophils: 60%). Six days after admission, the WBC count was within the normal range with 4.3/nL (neutrophils: 79%), accompanied by a decrease of G-CSF level (Quantikine HS Kit, R&D Systems, Wiesbaden, Germany) from 35.4 pg/mL on day 3 to 17.2 pg/mL on day 8 (5–95 percentile range 9.1–51.2 pg/mL in 37 normal persons). Shortly after cessation of clozapine administration a reexacerbation of the schizoaft-
fective symptoms was noted. Neuroleptic treatment with flupentixol (2.5 mg/b.i.d.) induced a severe hypokinesia with subsequent febrile urinary tract infection associated with an increase of C-reactive protein and WBC count (Figure 1). Flupentixole was stopped, and because of lack of alternative therapeutic options clozapine was reintroduced 4 days after cessation starting with 25 mg/day with a slow increase to 50 mg/day. This regimen led to an improvement of psychotic symptoms and hypokinesia. The infection resolved within 4 days under additional treatment with antibiotics. Symptoms of Parkinson’s disease resolved almost completely within the next 2 weeks, supported by L-dopa and metixen treatment. Close WBC monitoring was subsequently performed and WBC counts remained within the normal range including the last follow-up 36 months after the WBC drop (April 2000).

Discussion

In this case of granulocytopenia induced by clozapine treatment, we observed a rapid decrease of endogenous G-CSF levels with a normalization of neutrophil count after the clozapine treatment was discontinued. This suggests an intact regulatory mechanism of granulocytopenia, and therefore G-CSF therapy was not initiated. Despite the high risk for recurrence of granulocytopenia (Saffereman et al 1992), we decided to reintroduce clozapine because of a lack of alternative therapeutic strategies, considering that WBC was never below 2000/mm³. The G-CSF continued to decrease further, and the WBC increased following reintroduction of clozapine. This indicated stable bone marrow functioning in the patient.

During the entire clinical course the patient showed G-CSF values within the normal range according to the G-CSF-test kit manual and the literature (Watari et al 1989); however, a clear decline of G-CSF that was inversely correlated to an increase of WBC counts could be demonstrated, probably attributable to a delayed effect of G-CSF on WBC. This type of course involving a decline of G-CSF and a concomitant increase in the number of WBC is a well-known effect in bone marrow graft recipients. It occurs typically during a successful recovery of bone marrow function (Haas et al 1993). In the described patient we assume that the observed course of G-CSF and WBC counts represents an abortive form of toxic bone marrow damage with subsequent recovery indicated by an early inverse correlation of G-CSF and WBC counts.

This interpretation, however, should be viewed with caution for two reasons: First, the absolute G-CSF levels were lower compared to bone marrow graft recipients; and second, the observed fluctuations may be the effect of other factors, such as subsequent infections (Haas et al 1993). The described case nevertheless reveals that G-CSF levels may be a useful indicator for the follow-up of patients with suspected bone marrow damage due to clozapine. Further studies may also address the question of whether monitoring of G-CSF levels may be of help in the clinical decision of G-CSF treatment and clozapine rechallenge.

References


Lieberman JA, Yunis J, Egea E, Canoso RT, Kane JM, Yunis EJ (1990): HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry* 47:945–948.
