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Lamotrigine-induced leucopenia

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Lamotrigine (LTG), which is an anti-epileptic drug (AED) structurally similar to and derived from the dihydrofolate reductase inhibitor class of compounds, has a wide spectrum of anti-seizure activity and a favorable side effect profile (Czapinski *et al*. 2005, Messenheimer 1995, Ural *et al*. 2005). Rarely, hematological side effects including agranulocytosis, neutropenia, leucopenia and/or thrombocytopenia, aplastic anemia and asymptomatic disseminated intravascular coagulation have been reported (Damiani and Christensen 2000, Fadul *et al*. 2002, Czapinski *et al*. 2005, LeDrew *et al*. 2005, Messenheimer 1995, Ural *et al*. 2005). We report a patient who developed leucopenia after receiving LTG for complex partial seizures.

Case report

Our patient was a 24-year-old female with a diagnosis of epilepsy. For about 15 years, she has had complex partial seizures, three or four times yearly. Two years ago, she began barbexaclone (100 mg *tid*) and carbamazepine (CBZ; 400 mg *bid*) combined therapy. The patient attended our clinic with the complaint of increased seizure frequency. Her neurological examination and cranial MRI were normal. Her EEG showed single spike activity on the right temporal area, implying a focal abnormality. Routine laboratory studies revealed a white blood cell (WBC) count of 3.9 x 10^9/L (55% neutrophils and 32.7% lymphocytes). Other parameters were within normal ranges. LTG (25 mg/day) was added to the current barbexaclone plus carbamazepine combined therapy. Given the possible leucopenia-inducing effect, CBZ was gradually withdrawn from the current therapy during the third week and LTG dose was increased to 50 mg. However, partial seizures have persisted and the WBC count decreased to 2.7 x 10^9/L (51% neutrophils and 37.3% lymphocytes) at the third week. At the start of the fourth week, only LTG and barbexaclone were given. At the sixth week, the LTG dose was increased to 100 mg/day. There were no significant seizures, but the WBC count decreased to 1.9 x 10^9/L (49.3% neutrophils, 35.3% lymphocytes). As bone marrow aspiration showed a hypocellular pattern, LTG was stopped and clonazepam at a dose of 3 mg/day was added. Two weeks later, the WBC count had increased to 4.1 x 10^9/L (59.6% neutrophils, 38.3% lymphocytes) and clonazepam was stopped. Treatment was continued with Levetiracetam up to dose of 3000 mg/day plus barbexaclone at 300 mg/day dose, with good seizure control and normal WBC counts. It was concluded that bone marrow suppression caused by long term use of AED might have been prolonged by LTG, which may also cause leucopenia.

Discussion

The WBC count of our patient was slightly below the normal limit range during the barbexaclone plus CBZ combined therapy. Three weeks after LTG was started, the WBC count was considerably decreased. Despite the withdrawal of CBZ, which is a well known cause of leucopenia, the WBC count continued to decrease. It was only after LTG was stopped that the WBC count returned to the normal range. Taken together, these findings suggest that leucopenia induced by CBZ can be potentiated by LTG. The hematological side effects of LTG are controversial. Only a few studies have reported leucopenia and/or thrombocytopenia, agranulocytosis, neutropenia, aplastic anemia, bone marrow depression, pancytopenia and asymptomatic disseminated intravascular coagulation (Damiani and Christensen 2000, Fadul *et al*. 2002, LeDrew *et al*. 2005, Ural *et al*. 2005). Several cases of leucopenia have been reported so far. Risk factors include concomitant use of other AEDs, as in our patient, and doses exceeding the recommended initial dose or increments. However, the underlying mechanisms in LTG-related hematological complications are unknown. With regard to the fact that bone marrow suppression can occur as a result of long-term antiepileptic drug use, one must keep in mind that LTG treatment can lead to possible leucopenia in epileptic patients, who have a predisposition to leucopenia.

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