Case report

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Leucopenia and thrombocytopenia possibly associated with lamotrigine use in a patient

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ABSTRACT – Haematological side effects are rather exceptional with lamotrigine. We report the case of a 25-year-old woman with epilepsy who developed combined leucopenia and thrombocytopenia eight weeks after starting lamotrigine. Within weeks after lamotrigine was discontinued, all of the haematopoietic abnormalities had disappeared. To our knowledge, this is the first report of combined leucopenia and thrombocytopenia associated with lamotrigine treatment suggesting, in our patient, a causal reaction.

Key words: lamotrigine, epilepsy, leucopenia, thrombocytopenia

Lamotrigine (LTG; Lamictal®), a wide-spectrum antiepileptic drug (AED), is derived from the dihydrofolate reductase inhibitor class of compounds and is thought to act mainly through blocking the influx of sodium ions, thereby reducing excess glutamate release and stabilizing neuronal membranes (Leach *et al.* 1986). Lamotrigine is effective as monotherapy in both newly diagnosed adults with either partial or mixed seizure disorders and newly diagnosed children with absence seizures (French *et al.* 2004, I). It is also effective as an adjunctive treatment of refractory partial seizures and idiopathic generalized epilepsy in adults and children, as well as in the treatment of Lennox-Gastaut syndrome (French *et al.* 2004, II). It is eliminated mainly by hepatic metabolism to the glucuronide conjugate (Brodie 1992). Clearance of the drug is slightly lower in patients with Gilbert's syndrome, who have decreased uridine diphosphate glutamyl transferase activity (Peck 1991). LTG is well tolerated in children and adults (Arzimanoglou *et al.* 2001). The most frequent adverse events include somnolence, rash and episodes of transitory diplopia. It can very occasionally cause minimal haematological side effects, including agranulocytosis, neutropenia, thrombocytopenia and asymptomatic disseminated intravascular coagulation (DIC) (Nicholson *et al.* 1995, De Camargo and Bode 1999, Fadul *et al.* 1997, Mackay *et al.* 1997, Wong *et al.* 2001). We report a female patient who developed leucopenia and thrombocytopenia after receiving LTG for partial seizures.

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Case study

A 25-year-old woman was started on LTG (25 mg, *p.o.*, twice daily) because of simple, partial seizures. Her neurological examination and cranial MRI were normal; EEG showed left temporal focal abnormalities. LTG continued to be increased by 50 mg every two weeks up to 200 mg daily, because of progressively difficult-to-control, simple, partial seizures. Four weeks after starting LTG, she was clinically well and free of seizures. Laboratory studies revealed a platelet (PLT) count of 342 x 10^9/L and a white blood cell (WBC) count of 5.5 x 10^9/L with a normal differential. Four weeks later, at her routine follow-up, laboratory studies demonstrated a PLT count of 29 x 10^9/L and a WBC count of 1.7 x 10^9/L (neutrophils 0.8 x 10^9/L); her serum LTG concentration was 1.6 mg/L before taking LTG and 2.4 mg/L after 6 hours. Other laboratory values including hepatic, renal and thyroid function tests, antibody titers against rubella, toxoplasmosis, CMV, HSV, EBV, HCV, HIV and HBV, as well as the VDRL test, Melitensis, Wright and Gruber Widal agglutinations, ANA, anti-dsDNA, and anticardiolipin antibodies were all within normal limits. Antiplatelet and platelet-associated antibodies were negative. Examination of bone marrow aspirate revealed a hypocellular marrow with decreased, left-shifted myelopoiesis, a prominent increase in micromegakaryocytes with normal cytogenetics. The WBC and PLT counts, and the bone marrow features taken in conjunction with the absence of an infectious agent and immune etiology, suggested LTG-related, combined leucopenia and thrombocytopenia. LTG was discontinued immediately. One week later, follow-up laboratory studies revealed a PLT count of 127 x 10^9/L and a WBC count of 4.9 x 10^9/L (neutrophils 1.8 x 10^9/L), increasing to 237 x 10^9/L and 6.5 x 10^9/L, respectively.

Discussion

Existing AEDs have considerable potential for concentration-dependent and idiosyncratic toxicity (Brodie 1990). LTG was heralded as a promising new antiepileptic drug promoted on the basis of its effect on excitatory amino acid pharmacology, with a "low level of clinically significant side effects" (Brodie 1992). Most of the acute adverse reactions occur during the early stage of treatment, between one and four months (Wong *et al.* 2001). Haematological side effects among the 11,316 patients who were included in a non-interventional observational cohort study were insignificant (Mackay 1997). In that study, four cases of neutropenia, three cases of thrombocytopenia and two cases of DIC associated with LTG were reported. Thereafter, other cases of severe leucopenia have been reported (Nicholson *et al.* 1995, De Camargo and Bode 1999, Fadul *et al.* 2002, Solvason 2000).

In the patient we describe, combined leucopenia and thrombocytopenia developed eight weeks after starting LTG, by which time she was receiving 200 mg daily. The bone marrow features, WBC and PLT counts, the absence of an infectious agent and immune etiology, and WBC and PLT recovery after the LTG was discontinued suggest a causal relationship between the LTG and the combined leucopenia and thrombocytopenia.

Mechanisms responsible for LTG-related haematological complications are unknown. Risk factors thought to be associated with haematological effects include concomitant use of other AEDs, and exceeding the recommended starting dose or the recommended rate of dose escalation (Mackay *et al.* 1997). In our patient, there was no concomitant use of another AED, or indeed any other drug, or exceedance of the recommended starting dose of LTG. Although LTG was synthesized as one of a sequence of folic acid antagonists in response to the suggestion that folate was a proconvulsant, this property was not seen to alter haematological parameters in animal toxicology studies (Fadul *et al.* 2002). Idiosyncratic toxicity associated with LTG, characterized by a clinically significant increase in serum transaminase concentrations, haematological abnormalities, erythematous rash, nausea, and dizziness, has been reported (Nicholson *et al.* 1995), but in the patient we describe here, all of the laboratory studies were unremarkable and she was asymptomatic. A particular drug might bind to the membrane of circulating platelets, where it could then act as a hapten to trigger antibody formation (Levine 2004). However, in our patient, antiplatelet and platelet-associated antibodies were not detected.

In conclusion, there have been a few sporadic reports of isolated neutropenia or thrombocytopenia associated with the use of LTG over the past 10 or more years, however, this is the first report of combined leucopenia and thrombocytopenia associated with LTG treatment. □

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