

Switching from branded to generic antiepileptic drugs as a confounding factor and unpredictable diagnostic pitfall in epilepsy management

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Patients with epilepsy are frequently invited (often by their own GP) to switch from branded to generic anti-epileptic drugs. The main reason for this change in treatment is that generic drugs cost less, and this has important implications in health expenditure control. Despite the "essential similarity" of drugs, the prescription of generic products may, however, expose patients to additional and, in some cases, unpredictable risks (Crawford *et al.* 1996, Argumosa and Herranz 2005).

Some days ago, a 20-year-old female patient, who is being followed in our center because of drug-resistant partial epilepsy, presented a generalized tonic-clonic seizure despite being on treatment with carba-

mazepine (Tegretol) (CBZ) at a daily dose of 600 mg and levetiracetam (LEV) at a daily dose of 2 000 mg. Blood tests performed immediately after the seizure showed a CBZ plasma level of 40 $\mu\text{mol/L}$. In the two days following the seizure, the patient, who was waiting for a follow-up visit, complained of dizziness and presented a rapidly progressing ataxic syndrome with nystagmus, gait and stand disorder, cerebellar dysarthria and bilateral dysmetria; a concomitant confusional state and suspicious pyramidal signs consisting of tetra-hyperreflexia were noted. In view of the patient's CBZ plasma level and the abrupt clinical changes, a brainstem/cerebellar pathology was suspected and further investigations were performed: the MRI scan and EEG were unremarkable (rachicentesis was planned, but fortunately not performed). Further blood tests revealed a CBZ plasma level of 140 $\mu\text{mol/L}$. When the patient's history was investigated more thoroughly shortly after this second blood test, she mentioned that her GP had changed her treatment, switching from Tegretol to generic CBZ, at the same dose, some days prior to the onset of the ataxic syndrome. Following the withdrawal of generic CBZ, the patient's plasma level progressively decreased and the ataxic clinical signs gradually resolved. A diagnosis of CBZ intoxication was made and the patient's treatment was modified by adding Barbexalone to LEV. The figure 1 shows the most noteworthy phases during the management of the patient.

We hypothesize that the pharmacokinetic properties of generic CBZ (or others substances used as excipients),

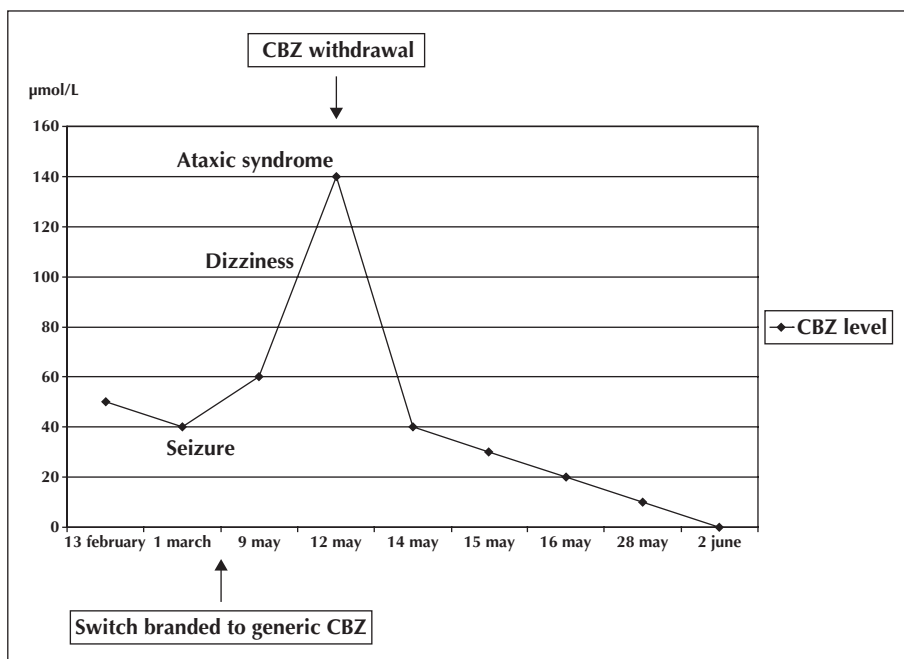


Figure 1. Graph showing CBZ plasma levels and related clinical findings prior to and during admission.

taken by our patient were different from those of Tegretol (Crawford *et al.* 2006), a hypothesis currently being investigated by further studies.

Following previous reports highlighting the risks of switching from branded to generic anti-epileptic drugs and the prudence recently recommended (Heaney and Sander 2007) concerning this issue, this case confirms the risks involved in such a change and justifies the distrust of patients who are asked to make this change (Andermann *et al.* 2007). Moreover, this report suggests that switching should only be undertaken after the treating neurologist has been consulted (in Italy, this change in therapy is usually encouraged by the GP or pharmacist) and a potential relationship between the "new" treatment and clinical changes (not only in terms of seizures, but of new signs and symptoms) should be considered. This case proves that the efforts of health administrations to reduce costs in clinical practice may sometimes be counterproductive, resulting in higher costs (e.g. hospitalization, further clinical investigations) (Crawford *et al.* 2006) and generating further insecurity in patients with epilepsy.

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References

- Andermann F, Duh MS, Gosselin A, *et al.* Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. *Epilepsia* 2007; 48: 464-9.
- Argumosa A, Herranz JL. The clinical and economic impact of generic drugs in the treatment of epilepsy. *Rev Neurol* 2005; 41: 45-9.
- Crawford P, Hall WW, Chappell B, *et al.* Generic prescribing for epilepsy. Is it safe? *Seizure* 1996; 5: 1-5.
- Crawford P, Feely M, Guberman A, *et al.* Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. *Seizure* 2006; 15: 165-76.
- Heaney DC, Sander JW. Antiepileptic drugs: generic *versus* branded treatments. *Lancet Neurol* 2007; 6: 465-8.