

More data on the safety of generic substitution

Yes, the blue tablet is OK?

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Seizures come out of the blue; people with epilepsy find themselves on classroom floors, on sidewalks, or in the emergency department (ED) after seizures and seek explanations for these sudden “breakthroughs.” A pharmacy replaces an effective white tablet with a blue one, leaving the patient anxious and uneasy—especially when the new tablet dissolves slightly more rapidly than the old one. And when the patient suddenly has a seizure, he or she concludes that switching between generic products is responsible.

Their assumption would seem to be clearly incorrect, given that the Food and Drug Administration (FDA) applies a bioequivalence (BE) standard in which approved generic copies must provide similar blood concentrations to reference (brand name) formulations. Small crossover pharmacokinetic studies are performed in healthy volunteers to show BE. And yet, many patients and case series by physicians report seizures after patients switch formulations and question whether the FDA’s BE standards with its 90% CI “acceptance range” is safe.^{1,2}

In this issue of *Neurology*®, Kesselheim et al.³ report findings that would seem to further contradict patients’ perceptions. They used a large Medicare database to show that ED visits due to seizures are not associated with patients switching between generic formulations of their antiseizure treatments and that changes in color and shape of tablets did not increase seizure risks. The raw data show a contradictory finding—that after their generic formulations were switched, patients had an 11% increased likelihood of ED visit due to seizures. This, however, appeared to be merely an effect of refilling prescriptions. Gagne et al.⁴ showed that refilling antiepileptic drugs (AEDs) increased odds for ED visits for seizures by 2.3×. This was attributed to various clinical factors: “delays in refilling, neurologic symptoms prompting the refill, or temporary nonadherence.”

The study by Kesselheim et al.³ is one of a number recently aimed at reviewing the overall safety of generic drug switching. The FDA sponsored 3 clinical BE studies to determine the adequacy of average BE studies for ensuring safe conversion between different anti-seizure products for patients with epilepsy. The Krauss

et al.⁵ modeling of BE study data suggested switches between disparate generic products (ones providing lower and higher drug concentrations compared to the brand reference) might cause 25%–30% shifts in drug concentrations, particularly for valproic acid and oxcarbazepine. Two completed FDA-sponsored clinical-pharmacology studies evaluated BE of lamotrigine. Ting et al.⁶ showed that Teva’s lamotrigine formulation and Lamictal provided similar concentrations during steady-state crossover exposures (90% confidence intervals [CI] for area under the curve [AUC], C_{max} and C_{min} varied <3% for the 2 formulations). Privitera et al.⁷ conducted a 4-period steady-state crossover study comparing blood concentrations of 2 different lamotrigine generic products: 90% CI for the ratios of AUC and C_{max} was ≤5% for the formulations. These 2 studies were informative for the practicing clinician, because in contrast to the typical FDA BE studies, they included adults with epilepsy of varying ages, taking a variety of concomitant medications, and receiving lamotrigine on a twice-daily basis. In addition, Privitera et al. compared the 2 most disparate generic products, presumably maximizing the opportunity to show a meaningful difference. Conceding the limitations of insurance databases, the Kesselheim et al. study showed that ED visits due to seizures are not associated with generic formulation switches (assuming the 11% increase was due to a refill effect).

Taken together, these studies confirm that most patients can safely switch between generic formulations, even between tablets differing in appearance.

So why do patients and open series report seizures associated with formulation changes? Probably several things are happening: (1) patients want to find a reason for the near random pattern of their seizures. Threshold cortical epileptogenic activity triggers seizures in near random patterns, with some effect of triggers (missing doses, stress, hormonal changes) influencing their timing⁸; (2) patients’ views towards illness and treatments might influence their reporting of seizures and drug effects.⁹ This search for seizure explanations can even extend to pets with seizures¹⁰; (3) there is temporal variability in individual drug absorption

See page 1796

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and elimination. Food has a major effect on absorption of antiseizure medications and C_{max} ; this is particularly common with modified release formulations.¹¹ A small subgroup of patients in FDA's clinical BE studies had variability in concentrations during re-exposure to the same product; and (4) a small group of patients may be outside the 90% CI BE acceptance range and may experience product switching effects—no such “outlier” patients were found in the lamotrigine study of Privitera et al. whereas Ting et al. found a single patient with a reduced generic-brand ratio (0.78). Patients vary widely in their susceptibility to seizures and adverse effects during antiseizure therapy; their seizures and medication effects may dominate clinical associations associated with shifts in drug concentrations in small subgroups.

So what should we do? Generic products are typically 75% cheaper than reference products and so should be used by most patients. Individual patients with seizures or possible adverse drug effects after formulation changes can be evaluated with seizure and pill-taking diaries and possibly with drug levels; individual dosing needs often dominate possible product switching effects. A small number of AEDs have complex kinetics (phenytoin) or variable absorption (carbamazepine)—it may be best to use single formulations of modified release formulations of these drugs along with careful clinical and laboratory monitoring. The most rigorous studies to date, including this one, suggest that generic antiseizure medication switching is safe, and reported “failures” after generic switches are generally not due to failure of the generic product itself to provide adequate blood levels.

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