Brief Communication

Therapeutic equivalency of generic antiepileptic drugs: results of a survey

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Abstract

Controversy persists whether generic antiepileptic drugs (AEDs) are interchangeable with brand name drugs with respect to efficacy and adverse events. Three hundred and one neurologists responded to a survey regarding generic AEDs mailed to 6420 neurologists, for an overall response rate of 4.7%. One hundred and ninety-six (67.8%) neurologists reported breakthrough seizures after a switch from a brand name to generic AED; 93 (32.2%) did not. One hundred and sixty-three neurologists (56%) reported increased side effects in their patients after a switch from a brand name to generic AED; 128 (44%) did not. Fifty-two (18.4%) neurologists agreed that the Food and Drug Administration standards for AED bioavailability are sufficiently narrow; 231 (81.6%) did not.

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1. Introduction

Generic antiepileptic drugs (AEDs) are commonly substituted for brand name AEDs. Indeed, 11 states mandate that pharmacists substitute a generic version of a prescribed drug if all prescription requirements are met [1]. According to the Food and Drug Administration (FDA), “If one therapeutically equivalent drug is substituted for another, the physician, pharmacist, and patient have the FDA’s assurance that the physician should see the same clinical results and safety profile” [2].

Despite this reassurance, both pharmacists and physicians have concerns about the substitution of generics for specific medications [3]. In particular, the narrow therapeutic range and low water solubility of phenytoin and carbamazepine, as well as the nonlinear pharmacokinetics of phenytoin, present significant issues regarding generic substitution [4]. According to the FDA, drugs that have a narrow therapeutic ratio, defined as “less than a 2-fold difference in median lethal dose \(LD_{50}\) and median effective dose \(ED_{50}\) values, or have less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration and patient monitoring,” are susceptible to “actual or potential bioequivalence problems” [5]. The FDA does not maintain a list of narrow therapeutic ratio drugs [2], but all AEDs would probably be included under this umbrella (personal communication, the FDA). Nonetheless, the FDA does not require more stringent bioequivalent requirements for generic substitution for narrow therapeutic ratio drugs, although it has allowed for this possibility [2].

2. Methods and analysis

A 13-question survey (Fig. 1) was designed for neurologists to assess the effects of generic substitution of AEDs on their patients with epilepsy in the past year.
The survey was mailed on 11 July 2003 to 6420 U.S. neurologists, whose names and addresses were obtained from a list broker. The last date of acceptance of results was 25 August 2003. A total of 301 (4.7%) neurologists responded (but every neurologist did not answer every question).

3. Results

One hundred and ninety-six (67.8%) of 289 neurologists reported breakthrough seizures and 163 (56%) of 291 neurologists reported increased adverse events after a switch from a brand name to a generic (Fig. 2). Ninety-three (32.5%) of 286 neurologists reported breakthrough seizures and 75 (26.6%) of 282 neurologists reported increased adverse events attributable to a switch from one generic AED to another generic AED (Fig. 2). Sixteen (6.2%) of 260 neurologists reported 1 patient, 123 (47.3%) neurologists reported two to four patients, and 73 (28.1%) reported five or more patients who encountered breakthrough seizures or adverse events due to switching to a generic in the past year, while 48 (18.5%) responded “N/A.”

Two hundred and sixty-two neurologists responded to the question (No. 7) regarding the consequences of generic drug substitution. One hundred and eighty-eight (71.8%) reported the need for extra phone consultations, 166 (63.4%) office visits, 128 (48.9%) emergency room visits, and 46 (17.6%) hospital admissions. Seventy-seven (29.4%) reported that patients missed work, 25 (9.5%) indicated that the doctor–patient relationship was undermined, and 23 (8.8%) reported patient injury (Fig. 3).

Two hundred and thirty-seven neurologists offered their response to these problems. One hundred and sixty-seven (70.5%) added “dispense as written” or similar instruction on future prescriptions, 88 (37.1%) neurologists changed the prescription to a formulation less likely to be substituted, 60 (25.3%) advised the patient to request the same brand of generic with each refill, and 17 (7.2%) advised patients to have blood levels monitored after each refill (Fig. 4). Two hundred and thirty-one of 283 (81.6%) neurologists disagreed with the
statement that FDA standards for bioavailability are sufficiently narrow, 209 of 282 (74.1%) disagreed that FDA standards ensure tolerability of generics, and 259 of 287 (90.2%) disapproved of generic substitution of AEDs by pharmacists without consulting the prescribing physician.

4. Discussion

The issue of generic drug substitution is complex and often poorly understood by physicians [6–8]. Although generic drugs must have the same active ingredient, inactive ingredients may differ. The range of 80–125% of acceptable bioequivalence required by the FDA is not evidence based, but was established by “medical experts” [9]. Bioequivalence studies for regulatory purposes are customarily performed in healthy adults, raising the question of their applicability to patients.

Another parameter that may affect bioequivalence is the amount and type of food taken with the medication. For example, Mylan received approval as a generic equivalent to Dilantin Kapseals based on bioavailability studies performed under fasting conditions [10]. However, a subsequent, single-dose, two-way crossover study of 24 healthy adults comparing the absorption of Dilantin Kapseals 100 mg to Mylan 100 mg after a high-fat meal revealed that the bioavailability (mean $C_{\text{max}}$) of Mylan was 13% lower than that of Dilantin Kapseals [10]. Because of phenytoin’s nonlinear kinetics, the researchers estimated that this difference could result in a median 37% decrease (19–58%) in plasma phenytoin concentrations, resulting in a drop below the therapeutic range in 46% of patients. Replacing Mylan with Dilantin Kapseals had the opposite effect; a 15% increase in bioavailability was estimated to cause a median 102% increase (range 24 to >150%) in plasma concentrations, resulting in 84% of the patients with phenytoin concentrations exceeding the therapeutic range [10]. Representatives from the FDA disagreed with these findings, citing errors in methodology and the fact that only 63 “lack of effect” cases due to Mylan had been reported [11].

The issue of interchangeability affects not only patients with epilepsy, but patients with other disorders as well. For example, patients taking generic fluoxetine have been reported to have lower efficacy, increased side effects, or both compared with patients taking brand name Prozac [12]. Similarly, after inadvertent substitution of generic clozapine for brand name Clozaril in 25 patients with schizophrenia, psychotic symptoms occurred in 7 (28%) previously well-controlled patients, 5 of whom required hospitalization. All 7 patients improved after reinstatement of the brand name drug [6].

The limitations of this survey must be recognized. The results are retrospective. No attempt was made to document each case by chart review. Neurologists may have attributed breakthrough seizures or side effects to generic substitution when in fact they were related to the natural history of the disease, intercurrent illness, poor medication adherence, or other factors. Conversely, some patients may have had breakthrough seizures or side effects attributed to other causes and not ascribed to generic substitution. Consequently, the number of true
generic substitution-related events may actually be higher or lower than reported.

With respect to the response rate of only 4.7%, the survey was mailed without an advance letter, it was not followed up by reminder letters or phone calls, and no compensation was offered, all of which could have potentially boosted the response rate [13]. The survey was confidential, but not anonymous, which may have deterred some potential responders.

Extrapolation of these results to the approximately 15,000 U.S. neurologists must be done cautiously. Responders may have been biased toward reporting problems with generics [13]. However, the survey reveals that at least (more than half of the doctors had more than one patient affected) 196 patients had breakthrough seizures in the opinions of their treating physicians due to substitution of generic drugs for brand name drugs, and 163 patients had increased side effects. Likewise, these physicians report that substitution of one generic for another led to 93 patients with breakthrough seizures and 75 with increased side effects. In addition to the patient morbidity and indirect costs resulting from additional seizures and adverse events, a rough estimate of the direct cost of 166 extra office visits ($120/visit), 128 emergency room visits ($750/visit), 2 and 46 hospitalizations ($12,154/visit), 3 totals $675,004. These results challenge the premise that generic substitution of AEDs for patients with epilepsy is cost-effective.

5. Conclusions

More than two-thirds of neurologists responding to this survey observed breakthrough seizures and more than half observed increased side effects due to generic substitution of AEDs. Although generic substitution of AEDs may be appropriate for many patients with epilepsy, there appear to be a substantial number of patients for whom generic substitution may represent suboptimal care. In these patients, potential cost savings of generic AEDs must be weighed against potential additional medical costs, such as extra office visits, emergency room visits, and hospitalizations. A prospective controlled evaluation of the therapeutic equivalency of generic AEDs in patients with epilepsy needs to be performed.

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References