Brand vs Generic Drugs: Are Patient Outcomes Affected?

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Question:

Do differences, if any, between generic and brand products affect clinical outcomes?

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Clinicians and patients often question the comparative safety and efficacy of generic substitutions vs their brand-name drug products. The US Food and Drug Administration (FDA) approves a generic substitute if it has proven to be "identical, or bioequivalent, to a brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use." [1] A drug is considered bioequivalent if it exhibits bioavailability properties (eg, rate and extent of absorption) that are similar to the product being compared. [2] The FDA requires that the 90% confidence interval of these properties fall within the 80%-125% range of the brand's. [2,3]

The FDA provides a coding system, called the *Orange Book* , to help practitioners identify (for substitution purposes) a product's therapeutic equivalence, which is considered as such when it is pharmaceutically equivalent and meets the same safety and efficacy parameters. [2] Drug products that the FDA consider therapeutically equivalent receive an A rating (followed by a letter designating its dosage form) if it meets the said criteria. An AB rating denotes products that have sufficient evidence to resolve any bioequivalence problems and are therefore considered therapeutically equivalent. However, it is also important to keep in mind that generic products are only compared with their brand products and not with the same product made by other manufacturers.

Drugs that are known to exhibit a narrow therapeutic index (NTI), such as levothyroxine and warfarin, are of greatest concern, despite FDA-approved therapeutic equivalence between brand and generic products. Because several formulations of synthetic thyroxine (T4) exist, their bioequivalence has been questioned. One particular study demonstrated that a few generic formulations were equivalent when compared with the original brand product. [4] However, when the FDA approved generic substitution for levothyroxine in 2004, several key organizations released a joint position statement recommending that patients continue to take what was initially prescribed; the methods used to determine bioequivalence did not account for endogenous T4 levels. [5] In addition, they recommend that if a formulation change is warranted, serum thyroid-stimulating hormone (TSH) levels should be retested in 6 weeks, considering that even the smallest changes in TSH levels can potentially result in adverse events. [5]

Another NTI medication whose generic bioequivalence has been scrutinized is warfarin. A systematic review and meta-analysis of 47 peer-reviewed publications found that, of the studies comparing generic warfarin with its brand product, clinical outcomes such as the international normalized ratio

(INR), dose adjustments, and adverse events were similar. [6] A retrospective analysis, however, discovered that switching between formulations appeared to be associated with increased risks for either a thrombotic event or bleed in patients using warfarin for atrial fibrillation; limitations inherent in retrospective analyses, including exclusion of concomitant use of medications, absence of adherence measures, and nonstandardized frequency of monitoring, may limit interpretation of the positive findings of this study. [7] Nevertheless, when considering changing from a brand-name product to a bioequivalent generic, or from one generic to another, it is recommended to monitor the INR of high-risk patients more closely.

The FDA determines the therapeutic equivalence of generic products to proprietary products on the basis of data supplied by the generic products' manufacturers; many are deemed substitutable for the branded versions. However, it is reasonable to heed caution when switching drug products within classes known to exhibit a NTI, particularly in the absence of a robust body of literature to suggest that clinical outcomes are affected. For these drugs, including levothyroxine and warfarin, adherence to monitoring at recommended intervals is especially important. [8]

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