Bioequivalence of Thyroid Preparations: The Final Word?

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The Food and Drug Administration's (FDA's) determination requiring that new drugs undergo extensive clinical testing to demonstrate safety and efficacy essentially eliminated, at least for a time, the possibility that medication would face competition upon patent expiry. The cost of fulfilling the requirements created a virtual monopoly—a boon for the established pharmaceutical industry but a politically untenable situation. In retrospect, the solution was a brilliant one. After horse-trading in Congress, the FDA elaborated a bioequivalence standard based on superimposability. If 2 orally administered products yield superimposable blood levels after a dose, then reason dictates that the 2 are therapeutically equivalent. This concept has been widely embraced because it is rooted in our current understanding of pharmacokinetics and pharmacodynamics.

As noted by Dr Bolton, in this series of reports, superimposability is based not only on inspection of the blood level time curves but also, more specifically, on the calculated average C_{max} and area under the drug concentration vs time curve (AUC). Furthermore, the FDA requires that 90% confidence intervals be placed on the ratio of test vs control products and that this interval is within 80% to 125% of the mean. To meet the second condition, the difference in average C_{max} and AUC of the 2 products is usually very small. Thus, the average differences in AUC values between a brand-name product and a generic product are typically 5% or less.

An objective analysis of the history of the bioequivalence standard must conclude that it has served us well. Hundreds of generic versions of drugs have been marketed with the approval of the FDA and with no adverse public health consequences. The debate over the therapeutic equivalence of generic drugs has been hushed, if not muted. Controversy, however, persists with regard to several types of drugs: those with a narrow therapeutic index (NTI), natural products, and those that have endogenous blood levels.

The FDA has dealt with the question of NTI in its evaluation and eventual approval of a generic version of the oral anticoagulant warfarin. The agency has demonstrated that it can certify NTI drugs with confidence of safety and effectiveness. Furthermore, in the future, drugs with as limited an individual dosing range as warfarin's are very unlikely to ever be developed.

The ability to declare the bioequivalence of natural products, because of the large number and variable amounts of constituents, continues to be a challenge. For this reason, there are no marketed versions of conjugated estrogens that are deemed therapeutically equivalent to and interchangeable with *Premarin* or *Prempro*.

Thyroid preparations have been the subject of the most recent debate over bioequivalence. While the FDA has treated the bioequivalence of levothyroxine products as a special case, the potency of levothyroxine products is no longer an issue and there is no evidence that it has an NTI. Nevertheless, many endocrinologists carefully titrate the dose of levothyroxine in hypothyroid patients, believing these measures are needed for safe and effective use. Further complicating matters is the fact that, except in patients with no thyroid function, levothyroxine is found endogenously in blood with varying levels. In the clinic, endogenous levels of thyroxine represent a significant fraction of total thyroxine levels during treatment.

There is now consensus that the impact of endogenous thyroxine levels on the estimation of bioavailability and bioequivalence can be substantially reduced in 2 ways: (1) by using a large dose of thyroxine in bioequivalency studies, rather than clinical doses; and (2) by applying an individual baseline adjustment. The FDA recommends a test dose of 600 μg; clinical doses range from 25 to 150 μg/day. The recommended baseline correction method is to subtract the mean of endogenous thyroxine levels at –0.5, –025, and 0 hours before dosing from each subject's thyroxine levels taken after dosing.

Evidence suggests that the current guidance gives unbiased estimates of bioequivalence. Dr Bolton cites a reanalysis by the FDA, using a baseline correction, of 4 submissions for levothyroxine in which 16 comparisons of doses (12 × 50 μg, 2 × 300 μg, and 6 × 100 μg) were made. Based on dissolution profiles, these comparisons were expected to show bioequivalence. The 90% confidence interval in all of these studies met the 80% to 125% criterion. The average of all the point estimates in these studies was 100.5%.

Based on the current guidance, the FDA has declared that several generic products containing levothyroxine are both effective and interchangeable with the leading brand of levothyroxine, Synthroid. Abbott, the maker of Synthroid, challenges this determination as do some prominent clinical endocrinologists. To support this contention, interested parties have submitted a Citizen's Petition. The brief contains the results of a study conducted by Abbott Labs in which otherwise identical levothyroxine products containing either 450 or 400 μg were

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compared as to "bioavailability," after baseline correction. Dr Blakesley describes and discusses the study in her report.

The expected ratio for C_{max} and AUC was 1.125. The measured ratios were 0.975 for C_{max} and 1.031 for AUC. Despite a 12.5% difference in "bioavailability," the 2 products met the criteria for bioequivalence. Clinical endocrinologists have interpreted these findings to mean that substitution of a generic levothyroxine product for Synthroid or another thyroid product may increase or decrease thyroxine levels by as much as 12.5%, after baseline correction.

This analysis, however, is misleading in that the FDA's guidance calls for a test dose of 600 μg, not 450 μg. The degree of "contamination" from baseline thyroxine levels to the blood level time course following administration of 450 μg levothyroxine is demonstrably greater than the degree of noise after administration of the recommended test dose; the lower doses are more likely to produce unreliable estimates of relative bioavailability. There is no evidence that the FDA protocol could result in the approval of generic levothyroxine products that differ from a standard by as much as 12.5%.

Although no direct evidence exists, the petitioners claim that a difference of 10% or more between levothyroxine products is clinically important and may result in loss of control in patients with hypothyroidism who are euthyroid because of treatment. Dr Green, in his article, speaks at length to this issue. It is not a simple one.

Information concerning the effect of a change in dose on thyroid control is limited, but one study, discussed in Dr Green's report, shows that an increase or decrease of 25 μg results in thyroid stimulating hormone (TSH) levels outside the euthyroid range. For a patient controlled with a 150-μg dose of a thyroid product, a clinically significant increase in TSH levels would require the substitution of a dosage form with a relative mean bioavailability of 85%. It is most unlikely that a levothyroxine product providing only 85% of the labeled amount would be judged bioequivalent to a product providing the entire labeled amount. Furthermore, most patients are controlled with doses even lower than 50 μg/day. Therefore, it is inconceivable that the substitution of one levothyroxine product for another, both of which meet the FDA's criteria for bioequivalence, will throw TSH levels out of kilter and result in clinical consequences.

Evidence suggests that physicians who treat patients with well-controlled uncomplicated primary hypothyroidism can be assured that no adverse consequences are likely to ensue by switching from one FDA-approved levothyroxine product to another. However, many physicians, especially clinical endocrinologists, are not assured and monitor patients more intensely and at greater cost when levothyroxine products are changed. Nearly all would strongly prefer to prescribe a single levothyroxine preparation and keep their patients on that preparation for the rest of their lives.

The only way they can do that is by prescribing a branded product. Given the fact that pharmacies continually seek to acquire and dispense the least-expensive marketed levothyroxine product, patients are likely to receive different preparations of the drug not only each time a new prescription is written but sometimes from refill to refill. This practice, which demands examination, is disconcerting to physicians and can cause panic in patients. The problem applies to almost all generic products. Physicians may be more concerned about thyroid than other generic drug products, but this concern may be reinforced by marketing tactics.

Perhaps, in time, through education, confidence in the FDA's certification process for bioequivalent preparations of levothyroxine will grow and prescribing attitudes will change. In the short term, however, we will see third-party payers continue to insist on the prescribing of the least-expensive levothyroxine product. This inevitably will lead to patients taking multiple preparations of levothyroxine during treatment. Physicians will continue to resist, even to the point of urging insured patients to accept higher copays for a branded product. And, rest assured, the burden will be heaviest on the needy and uninsured.