FDA Panel Scrutinizes Thyroid Drug Stability

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GAITHERSBURG, MD. — A 10% loss in potency over the shelf life of levothyroxine sodium products—the maximum amount allowed under current regulations—raises clinically significant concerns, and current potency specifications for these products should be tightened, according to a majority of two Food and Drug Administration advisory panels.

At a joint meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee and its Advisory Committee for Pharmaceutical Science, panelists recommended in a 25-1 vote, with one abstention, that the potency specifications for levothyroxine products should be narrowed to a maximum loss of 5% over a product's shelf life. This would correspond to a 95%-105% potency specification (where the product must contain 95%-105% of the amount in the label until the expiration date, rather than the 90%-110% allowed under the current standards).

Representatives of three manufacturers—Mylan Laboratories Inc., Abbott Laboratories, and Genpharm Inc.—said that the companies supported the panel recommendations and had the capacity to meet the proposed new standard. The FDA usually follows the advice of its advisory panels, which are not binding. Jane Axelrad, associate director for regulatory policy at the FDA, said the agency could set a schedule to meet these requirements that would avoid disrupting the supply of these products.

Panelists also questioned the methods used to assess potency and deterioration of these products in the stability studies, submitted by the manufacturers of the seven marketed levothyroxine products at the FDA's request. The studies, which found up to 10% loss in potency over 8-12 months in some products, were conducted under controlled conditions at room temperature, and did not reflect real-life situations such as opening a bottle twice a day for several months; leaving it open; exposing the pills to moisture such as during steamy showers in bathrooms; transport; and other factors that can hasten pill degradation.

During the open public hearing session of the meeting, representatives from the Endocrine Society and the American Association of Clinical Endocrinologists (AACE) brought up the issue of bioequivalence between the products.

Bioequivalence between products is really a bigger issue than stability, according to several speakers. It's 'the 800-pound gorilla in the room.'

Background documents provided by the FDA stated that the agency acknowledges that "substantial variability in potency between levothyroxine sodium products … could raise clinical concerns," but that it was "fundamental to first understand and to properly control consistency of dosing within a given product over time from prescription to prescription …before contemplating any action related to relationships between products."

Levothyroxine sodium, a drug with a narrow therapeutic index, is widely prescribed for thyroid disorders, with more than 13 million prescriptions in the United States and about 1 of every 19 Americans taking levothyroxine daily, according to the FDA.

The stability studies submitted by the manufacturers evaluated the potency of all 12 tablet strengths of products at room temperature for lots manufactured between June 2003 and June 2005; the results disclosed at the meeting were blinded so that no product names were given.

Results were provided for three different strengths: 100 mcg and 125 mcg, the most widely prescribed strengths, and 25 mcg, prescribed to vulnerable populations, such as newborns and the elderly. For some products, there was up to a 10% loss of potency during the shelf life of a product, over 8-12 months, according to Eric Duffy, Ph.D., director of the division of postmarketing evaluation in the FDA's Office of New Drug Quality Assessment. Therefore, theoretically, a tablet could degrade to the point where it contained less thyroxine than a lower-strength tablet. For example, if a 150-mcg tablet lost 10% of its potency, it would contain 135 mcg of the active ingredient, which is below the 137-mcg dose, the next lowest available dose; this actually occurred in two stability studies, Dr. Duffy said.

Because these studies were done under ideal situations, with controlled temperature and humidity, it can be assumed that the "real-life stability profile" of these products would not be better than what was observed in these stability studies, he added. Levothyroxine tablets are typically subjected to a variety of factors that could affect stability, from the time the product is shipped from the manufacturer until it reaches the patient, with time spent in the warehouse, mailboxes, and pharmacies. Patients also store their tablets in various ways, often in a warm, moist environment such as a bathroom, but levothyroxine is known to be stable only when stored under tightly controlled conditions, in a sealed container, at or below room temperature, and kept dry.

"We have to ask for a higher set of standards" for a drug that comes in 12 dosage strengths and has such a narrow therapeutic index, said panelist Dr. Morris Schambelan, chief of the division of endocrinology at San Francisco General Hospital. Dr. Robert Tuttle, of the endocrine service at Memorial Sloan Kettering Cancer Center, New York, remarked that there was "no question" that a 10% change in dose would make a difference clinically in thyroid cancer patients, who take levothyroxine under very controlled conditions.

Panelist Arthur Kibbe, Ph.D., of the Nesbit School of Pharmacy, Wilkes University, Wilkes-Barre, Pa., said that if the potency levels of all these products on the market were tightened, the possibility of differences between products would also be lessened and would reduce the chance of adverse effects of switching from one product to another.

Dr. Jurgen Venitz, of the Virginia Commonwealth University School of Pharmacy, Richmond, said that as much as he supported the panel's recommendations, he felt that bioequivalence between products was really the bigger issue. One panelist referred to bioequivalence as "the 800-pound gorilla in the room."

Speaking for AACE during the open public hearing, Dr. Jeffrey Garber, treasurer and chief of endocrinology at Harvard Vanguard Medical Associates, Boston, said that it has become "increasingly unlikely" that a patient will be given a therapeutically equivalent preparation, and that while the meeting was "a step in the right direction," it did not address the broader issue of bioequivalence.

Speaking for the Endocrine Society, Dr. Leonard Wartofsky, president of the society, said that current FDA bioequivalence standards are not sensitive enough to detect small but meaningful differences between products, and that the FDA erred in allowing manufacturers to drop the warning that when a product is switched, patients need to call their physician and have their thyroid-stimulating hormone levels measured to retitrate their dose. He referred to a May 2005 meeting cosponsored by the FDA, American Thyroid Association, Endocrine Society, and AACE to review concerns about substitution and bioequivalence, and concerns that one product may be substituted for another—often unbeknownst to the physician—despite differences in potency. ■

Skin Blisters a Side Effect

Thyroid *from page 1*

The last three patients in the series—who received the highest concentrated dose of ultrasound waves—showed complete coagulative necrosis in 75% of the targeted area. These patients also received local anesthesia.

"High-intensity focused ultrasound allows us to destroy a very precise area," Dr. Esnault said. "It is an exciting procedure for thyroid nodule management, and it is a logical step when you are aware of technology."

The HIFU treatment is done using real-time ultrasound imaging. The HIFU transducer emits a beam of convergent ultrasonic waves toward the target tissue. When the ultrasound waves first enter the tissue, the beam is wide, so the density is low and the waves do not damage the superficial structures. But when the beam converges on the target, the density increases, and the tissue coagulates in a few seconds.

The beams are repeated at short intervals to achieve complete nodular destruction.

Overall, patients tolerated the treatment well. Seven patients experienced superficial skin blisters that subsequently healed, and the design of the treatment device has since been modified to reduce the risk of blistering, Dr. Esnault said. Three patients chose to stop the treatment because they felt "uncomfortable or scared."

There was an increase in thyroglobulin in six cases at 1 day after the procedure, but the change was transient. No changes were observed in other thyroid hormones, including T_3 and T_4, as a result of HIFU.

Caveats of the study included the fact that some patients got stronger doses of ultrasound than others. "It was not always possible to deliver the fully planned energy amount for maximum efficiency, due to slight skin breaks," Dr. Esnault said.

But data from additional patients who have been treated in this ongoing phase II study confirm that skin tolerance is good at high energy levels, he added.

Although the HIFU treatment has been used only on benign thyroid nodules so far, HIFU is used to treat prostate cancer, and it can probably be used to treat thyroid cancer in the future, Dr. Esnault said. "We just treated benign nodules, so we didn't worry about margins, but if you need a margin you can obtain it," he said. A big difference between HIFU and other ablative techniques is the high degree of precision that HIFU accords, he added.

The researchers have not studied the DNA or any other characteristics of the nondestroyed tissue surrounding any of the HIFU-treated nodules to look for adverse effects, but the pathologist did not observe any changes in the surrounding tissue, he noted.

Results from a literature review published in 2003 suggested that high-intensity focused ultrasound would have a significant impact on all fields of surgery, including thyroid surgery (Br. J. Radiol. 2003;76:590-9). Although a controlled study and long-term follow-up are necessary next steps, these early findings help establish safety, efficacy, and the treatment parameters for the use of HIFU on benign thyroid nodules, Dr. Esnault said.

Dr. Esnault has an ownership interest in Theraclion, the manufacturer of the HIFU that was used in the study. ■

COURTESY DR. OLIVIER ESNAULT/SAINT LOUIS HOSPITAL

An ultrasound shows the HIFU beam converging on the tissue target.