# Communications

# Equivalence of Various Levothyroxine Preparations

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It has previously been reported that levothyroxine preparations distributed by various manufacturers may not be therapeutically[1-4] or biochemically equivalent.[3,5] Others have reported no difference between two common brand name levothyroxine products.[6,7] Manufacturers have been reported to meet all the analytical standards required by the United States Pharmacopeia (USP).[8]

In order to help clarify the significance of these various reports, five different brands of levothyroxine tablets were administered in random order to ten hypothyroid patients. Physical tests were also performed on each brand according to USP standards.

## Methods

Ten hypothyroid women with an average age of 41 years (range 29 to 58 years) without goiter entered the study. All patients were well controlled with 100 to 200 $\mu$g daily of levothyroxine. Patients had been on a consistent dose of levothyroxine for at least two years prior to entering the study. They were treated for six-week periods on their usual daily dose of levothyroxine with products A, B, C, D, and E. Patients were randomly assigned to a treatment group according to a 5×5 Latin square design. Five levothyroxine preparations were studied:

Drug A: Lett-1 (sodium levothyroxine 0.1 mg), Scrip Laboratories, Peoria, Ill, lot No. 91040 (generic)

Drug B: Sodium levothyroxine 0.1 mg, Western Reserach Laboratories, Denver, Colo, lot No. D-602 (generic)

Drug C: L-Thyroxine Sodium 0.1 mg, Rugby Laboratories, Rockville Center, NY, lot No. 001010 (generic)

Drug D: Synthroid (sodium levothyroxine 0.1 mg), Flint Laboratories, Deerfield, Ill, lot No. ZD178

Drug E: Levothyroid-1 (sodium levothyroxine 0.1 mg) Armour Pharmaceutical Co, Phoenix, Ariz, lot No. T30404

Subjects received a 60-day supply of each product and were instructed to return to the clinic in six weeks. Patients were instructed not to take their levothyroxine on the morning of the clinic visit so that each blood sample could be drawn 24 hours after the last dose. This procedure allows six weeks during which the patients reach steady state blood levels with each brand. Drawing blood samples 24 hours after the last dose represents a steady state concentration without the interference of absorption variability. Serum thyroxine ($T_4$),[9] serum triiodothyronine ($T_3$),[9] and thyroid stimulating hormone (TSH)[10] were measured by radioimmunoassay at each visit. All samples were analyzed by the laboratory at the University of Mississippi Medical Center, Jackson, where normal values for $T_4$ are 6 to 13 $\mu$g/100 ml, for $T_3$ are 0.8 to 2.0 ng/ml, and for TSH are 2 to 10 $\mu$IU/ml.

Compliance checks were performed at each

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visit by means of a tablet count on return medication. No patient missed more than three tablets during any six-week trial period.

Medications were packed by the pharmacy so that the investigators could not identify the drugs. Tablets with identification marks could be identified by the patients if they desired.

Since doses of levothyroxine between 100 to 200 μg were used, values for both $T_3$ and $T_4$ were normalized for each patient by setting the minimum serum level equal to 1.00 and mathematically determining the other values for a given patient. The means for the normalized values were calculated and compared using a Duncan multiple range analysis.

Sodium levothyroxine tablets were obtained from five different manufacturers by purchase through the pharmacy at the University of Mississippi Medical Center. A sufficiently large sample of each product was purchased so that all tests were performed with tablets from the same lot. One hundred tablets were used for in vitro testing, and the rest were used for the human study portion.

Six standard physical tests were performed on the five lots of sodium levothyroxine. Twenty tablets of each lot were weighed on a Mettler A 30 balance (model No. 743022). The average weight and standard deviation were calculated. The tablets were also measured for diameter and thickness using a micrometer (White-Gun). The hardness of the tablet was determined using a Schienger hardness tester (model 2E/106, series 7410). Ten tablets from each group were tested, and the average and standard deviation were calculated. The hardness is reported in Strong Cobb units. Ten tablets from each lot were also tested for time to disintegration using a USP disintegration testing apparatus according to the USP method.[11] The tablets were also tested for loss of weight with handling or friability. Twenty tablets were weighed and placed in a Smith Kline & French fribilator for ten minutes, after which they were reweighed and the loss of weight reported.

## Results

Thyroid stimulating hormone, serum $T_4$, or serum $T_3$ levels did not change significantly in any patient. Patient 5 was removed from the study because she became pregnant and the dose of levothyroxine changed. Brands D, E, and A were taken before she became pregnant, with $T_4$ levels being 7.3 μg/100 ml, 7.7 μg/100 ml and 7.5 μg/100 ml, respectively.

The Scrip Laboratory product showed the greatest number of low values, which were not significantly different from the other products tested when a Duncan multiple range test was performed in addition to the basic t tests for differences within means. There was no statistically significant difference between any of the products. There were obvious differences in the size and weight as well as other physical tests between different brands, but these seem to have no effect on serum $T_4$ and $T_3$ levels. All of the physical tests fell within USP limits for all the brands tested.

## Comment

The results show that all the brands tested are equally bioavailable in patients. The physical tests cannot be used to predict bioavailability. The Armour product was significantly superior in these tests (lower friability and faster disintegration) but demonstrated no difference in bioavailability.

Previous reports examining bioavailability among different brands of levothyroxine were either anecdotal,[1,2] compared only three or fewer brands[3,4,6,7] or had few patients.[3] Some reports were not randomized,[1-4] not blinded,[1-4] did not perform compliance checks,[1-4] or did not give sufficient information on procedures, such as standardizing blood drawing time.[1-4,6,7]

It should not be concluded that all levothyroxine preparations are equivalent. The five brands tested were equally bioavailable and could be substituted for one another. There was, however, some individual variation in both $T_3$ and $T_4$ serum levels among the different brands tested, although this was statistically not significant. At least 17 different brands of levothyroxine are available,[2] and since studies on other brands have been variable, health practitioners are best advised only to substitute brands shown to be equivalent in clinical studies.

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# Psychotherapeutic Intervention and Health Service Utilization

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The value of brief psychotherapeutic or mental health interventions in reducing health service utilization by emotionally distressed persons has been studied by many investigators.[1-7] The psychotherapeutic intervention common to all these investigations was continuing talk sessions with the same person.

The accumulating evidence on the value of simple mental health interventions in reducing utilization is inconclusive. Taken as a whole, the literature provides little assurance that the mental health intervention of various studies is comparable. At best, the studies measure the number of mental health visits vs any qualitative estimation of the nature and type of service provided.

The majority of studies[2,4-7] measured patients' use of health service the year before and the year after the experimental maneuver. Of these, one study[5] had no control group and several investigations[4,7] suffered from a lack of comparability among study groups. Investigations by Follette and Cummings[1] and Kogan et al[3] met the more rigorous criteria of comparable study groups, a cohort analytic study design and multiple years of utilization measured. If the methodological question of the number of years to be measured when the outcome variable of health service utilization is examined, it could explain the mixed results of these studies.

The basic purpose of this study was to determine the effect of an ongoing physician-patient relationship on health service utilization in a prepaid practice. Does the health service utilization of persons who receive most of their primary care from the same professional differ from that of persons who receive care from any one of 12 professionals?

## Method

In May and June of 1979, the records of 9,317 patients in four family practices grouped as a health service organization (HSO) on a global budget* were enumerated (classified as to age, sex, and family practice and emergency health service utilization) during the preceding year.

A cohort of 419 frequent attenders were identi-

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*Physicians on a form of remuneration other than fee-for-service were needed for this demonstration. If the physicians were on a fee-for-service system, there may have been a financial motive for allowing patients to come back frequently.

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