Bioavailability of Thyroid Hormones From Oral Replacement Preparations

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We evaluated gastrointestinal absorption in normal subjects of T_4 and T_3 from synthetic T_3 tablets (Cytomel^R, SKF), desiccated thyroid tablets (Armour), thyroglobulin tablets (Proloid^R, Warner-Chilcott) and synthetic L-T_4 tablets (Synthroid^R, Flint and Levothroid^R, Armour). Measurements of serum T_4 and T_3 concentrations and free hormone indices were made at multiple times after tablet ingestion, and T_3 content in tablets was measured by radioimmunoassay. The time to peak serum T_3, and the 26 hr integrated increment in serum T_3, corrected for the amount of T_3 ingested, were not significantly different for 75 μg of synthetic T_3, 6 grains of desiccated thyroid (containing 99 μg T_3) and 5 grains of thyroglobulin (containing 90 μg T_3), the mean integrated increment values for the biological preparations being within 12% of those for synthetic T_3. The peak serum T_4 concentration, the time to peak T_4, and 48 hr integrated increments in serum T_4 and T_3 were similar after 3 mg of Synthroid^R and Levothroid^R. The mean peak serum Free T_3 Index after 75 μg T_3, 500, was much higher than the mean peak Free T_3 Index after 3 mg T_4, 290. The time to peak Free T_3 Index was much less after 75 μg T_3, 2 hr, than the time to peak after 3 mg T_4, 2 days. These results indicate that the time course and extent of T_3 absorption do not differ, whether the T_3 is given as the synthetic iodothyronine or as part of the thyroid protein, thyroglobulin. This approach appears to be useful in determining bioavailability of thyroid hormones from oral preparations and to assess the possibility of thyroid hormone malabsorption.

ALTHOUGH MILLIONS of doses of biologically-derived thyroid hormone tablets, either desiccated thyroid or thyroglobulin, are taken each year by hypothyroid patients, the bioavailability of hormones in these preparations are not well defined. The content of T_4^* and T_3^* in these preparations can vary widely, even when the USP standards† for iodine content are met.[1-4] Analyses in our laboratory have shown that Armour desiccated thyroid and Warner-Chilcott thyroglobulin (Proloid^R) have a low between-batch variation in the T_4 and T_3 content per tablet.[1] There are no standards for evaluating biological potency or bioavailability of thyroid hormone preparations in man. In a recent study, Armour desiccated thyroid and T_4 were compared in terms of their relative potency in suppressing basal and TRH-stimulated TSH secretion in hypothyroid patients.[5] The authors concluded that T_4 is approximately 1000 times as potent as desiccated thyroid on a weight basis. Accordingly, 1 grain of desiccated thyroid (≃60 mg) would be as potent as 60 μg T_4. However, our previous results[1,2] indicate that 1 grain of Armour desiccated thyroid contains 58–65 μg of T_4 and also 12–15 μg of T_3. This comparison raised the question of whether the bioavailability of T_4 and T_3 is less in the biologically derived preparations than in the synthetic ones. In addition, the possibility has been raised that differences exist in the bioavailability of T_4 from tablets of two widely used brands of synthetic T_4.[6] To clarify these questions regarding the bioavailability of orally administered thyroid hormones, we studied the acute changes in serum T_4 and T_3 concentrations after single doses of synthetic T_4, T_3, desiccated thyroid and thyroglobulin in normal subjects.

MATERIALS AND METHODS

To compare T_3 absorption from tablets of synthetic T_3, desiccated thyroid and thyroglobulin, healthy male volunteers, receiving no medications, were admitted to the Clinical Research Center of Brigham and Women's Hospital. After an overnight fast, the subjects received three 25 μg T_3 tablets (Cytomel^R, Smith, Kline and French), five 1 grain thyroglobulin tablets (Proloid^R, Warner-Chilcott) or three 2 grain desiccated thyroid USP tablets (Armour). The T_3 was given first and one other preparation was given at least three days later. Two subjects received T3 and thyroglobulin, two subjects received T3 and thyroid USP, and two subjects received all three preparations. Each preparation was administered at 0800 h with 200 ml water. Blood samples were obtained 15 min and immediately prior to tablet ingestion and 1, 2, 3, 4, 6, 8, 10, 24, and 26 hr thereafter. The subjects ate lunch at 1200 h, supper at 1700 h and a snack at 2200 h but ate nothing else on the days of tablet ingestion. Seventy five μg T_3 was chosen since there is a substantial increment in serum T_3 after ingestion of this dose, and the amounts of desiccated thyroid and thyroglobulin doses were selected to have a similar amount of T_3, based on our previous assays.[1]

To assess hormone absorption from synthetic T_4 tablets, three healthy male volunteers ingested thirty 0.1 mg T_4 tablets in 2–3 min (Synthroid^R, Flint or Levothroid^R, Armour). The doses were administered at least 4 wk apart. Two subjects were given the Flint preparation first and the other subject was given the Armour preparation first. Blood samples were drawn at 15 min and immediately before tablet ingestion and at 1h, 2h, 4h, 6h, 24h, 2d, 4d, and 7d

*T_4 and T_3 are used to denote the levorotatory (L) isomers throughout this report.

†These standards apply to both desiccated thyroid and thyroglobulin.

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afterward. Food intake was ad lib after 1200h on the day of tablet ingestion. These protocols were approved by the Brigham and Women's Hospital Human Subjects Committee, and informed consent was obtained from the subjects.

Serum T_3 and T_4 were measured by radioimmunoassay.[7] All the samples from each subject were measured in a single assay, and sera were diluted, when necessary, in iodothyronine-free serum to fall on the optimal portion of the assay standard curves. Serum protein binding was assessed by a normalized charcoal T_3 uptake. Free T_4 and free T_3 indices were calculated by multiplying the total serum concentration of T_4 or T_3 by the charcoal T_3 uptake. These indices were not given units. Normal ranges in this laboratory are T_4, 5.0–10.2 μg/dl, T_3 75–225 ng/dl, free T_4 index 4.7–10.5, free T_3 index 70–215, normalized charcoal T_3 uptake 0.85–1.10. The T_3 content of the tablets was determined by radioimmunoassay of Pronase® digests of the tablets.[1]

The integrated T_3 or T_4 absorption was the area under the curve of serum T_3 or T_4 versus time, from which the basal area (mean of the −15 min and the 0 time concentrations multiplied by the time) was subtracted. Areas were calculated by the method of trapezoids. Statistical comparisons were made by analysis of variance with linear contrasts, or the t test, as appropriate. Results are expressed as mean ± SEM.

RESULTS

Serum T_3 and T_4 Following T_3, Desiccated Thyroid, and Thyroglobulin

Serum T_3 concentrations after ingestion of 6 grains of desiccated thyroid and 75 μg of T_3 are shown in Fig. 1. For both desiccated thyroid and T_3, individual subjects' serum T_3 levels peaked between 2 and 4 hr, then progressively declined. In these subjects, the mean peak serum T_3 concentration following desiccated thyroid was 640 ± 48 ng/dl and the mean peak serum T_3 concentration after T_3 was 552 ± 61 ng/dl. Table 1 shows that the integrated T_3 absorption from T_3 and desiccated thyroid tablets did not differ significantly, whether expressed per total dose or per μg T_3 ingested.

Serum T_3 concentrations following ingestion of 5 grains of thyroglobulin and 75 μg T_3 are illustrated in Fig. 2. In this group of subjects, the mean peak serum T_3 concentration following thyroglobulin, again occurring between 2–4 hr, was 573 ± 46 ng/dl and that after 75 μg T_3 was 477 ± 15 ng/dl. The integrated T_3 absorption per total dose from T_3 and thyroglobulin tablets differed signficantly, $p < 0.05$ (Table 1) but this difference was due to the difference in T_3 content of the tablets (Table 1), inasmuch as the integrated T_3 absorption per μg T_3 in the tablets did not differ between the T_3 and thyroglobulin preparations.

Serum T_4 Following T_3, Desiccated Thyroid and Thyroglobulin

The expected T_4 content of 6 grains of desiccated thyroid is 363 μg and that of 5 grains of thyroglobulin is 275 μg.[1] Fig. 3 demonstrates serum T_4 concentrations following T_3, thyroglobulin and desiccated thyroid. The peak increment in mean serum T_4 following desiccated thyroid was 4.1 μg/dl at 2 h, and that following thyroglobulin was 1.8 μg/dl at 3 and 6h. The increases in serum T_4 after desiccated thyroid and thyroglobulin were significant ($p < 0.01$) when the −30 min and 0 min values were compared to subsequent values by analysis of variance. There was no significant change in the serum T_4 after administration of T_3.

Serum T_4 Following 3 mg T_4

After a 3 mg dose of Synthroid or Levothroid, there was a rapid increase in the mean serum T_4 concentra-

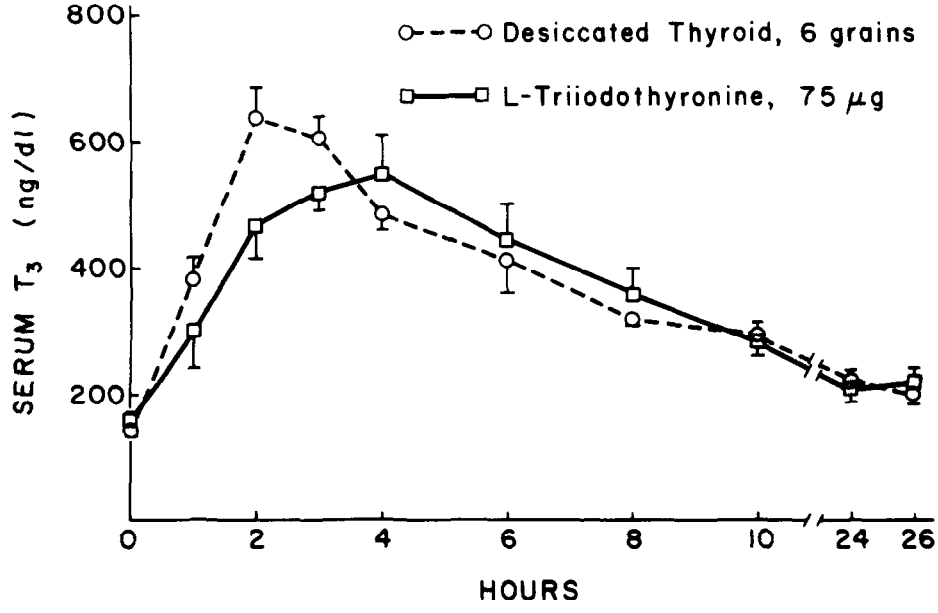

Fig. 1. Serum T_3 concentrations after oral T_3 and desiccated thyroid. Four subjects received 75 μg T_3 on one occasion and 6 grains desiccated thyroid (T_3 content 99 μg) on another. Points indicate mean ± SEM.

Table 1. Integrated T_3 Absorption Over 26 hr After Oral T_3, Desiccated Thyroid or Thyroglobulin

Dose	A T_3 Content of Tablets	B T_3 Content of Total Dose	C Integrated T_3 Absorption	D Integrated T_3 Absorption per μg T_3
	μg/tablet	μg	ng T_3 · hr/dl	B/C
Study 1				
6 grains desiccated thyroid (three 2 grain tablets)	33 ± 1	99	4,540 ± 260	46 ± 3
75 μg T_3 (three 25 μg tablets)	25 ± 1	75	3,930 ± 320	52 ± 4
p			NS	NS
Study 2				
5 grains thyroglobulin (five 1 grain tablets)	18 ± 1	90	4,100 ± 290	46 ± 3
75 μg T_3 (three 25 μg tablets)	25 ± 1	75	3,500 ± 390	47 ± 5
p			<0.05	NS

Results are mean ± SEM. The T_3 content of three tablets of each drug was measured by radioimmunoassay, and the results multiplied by the number of tablets administered. In each study, four subjects received T_3 on one occasion and the biologically derived preparation on another.

tions to respective maximums of 27.7 ± 1.1 μg/dl and 24.9 ± 4.4 μg/dl at 4h (Fig. 4). At each time up to 2 days, the mean serum T_4 concentrations after Synthroid and Levothroid were quite similar, as were the integrated T_4 absorption values (Table 2). With all six absorption studies combined, there was an exponential decrease in the T_4 increment between 4 hr and 7 days with a $t_{1/2}$ of 2.7 days. Despite the transient high serum T_4 concentrations, the subjects had no symptoms of hyperthyroidism or change in resting pulse.

Serum T_3 Following 3 mg T_4

Fig. 4 demonstrates the serum T_3 concentrations following 3 mg Synthroid and 3 mg Levothroid. There was no significant early peak in T_3 2 hr after the T_4 dose. The earliest significant increase in serum T_3 was at 4h, and the peak mean serum T_3 level following both T_4 preparations, 78%–80% over the baseline, occurred at 2 to 4 days, with a subsequent gradual decrease to a serum T_3 concentration 31%–35% above baseline at 7 days. The mean integrated increments in serum T_3 concentrations in the first 48 hr after T_4 (representing absorbed T_3 and T_3 derived in vivo from T_4) were not different after Levothroid and Synthroid (Table 2).

Free Hormone Index Measurements

Changes in the Free T_4 Index and the Free T_3 Index following 3 mg of T_4 and 75 μg of T_3 are illustrated in Fig. 5. The mean normalized T_3 charcoal uptake rose from a baseline value of 0.99 to a maximum of 1.53 at 2–4h after the T_4 dose. As a consequence, the five-fold increase in the mean Free T_4 Index following 3 mg of Levothroid or Synthroid (Fig 5) was greater than the three-fold increase in the mean total T_4 (Fig. 4). Similarly the 2.4-fold maximum increase in the mean Free T_3 Index at 2d was greater than the 1.8-fold maximum increase in the mean total T_3. After 75 μg T_3, with data of all subjects pooled, the mean normal-

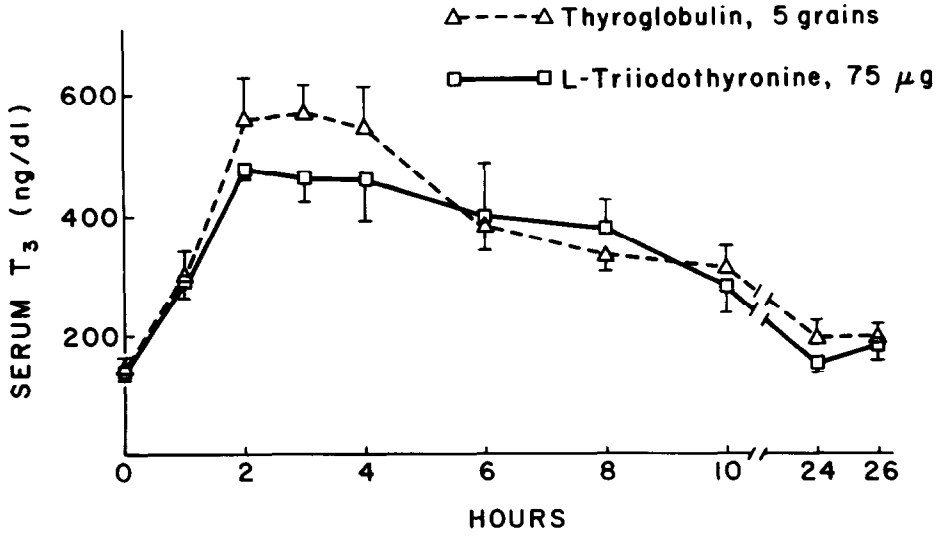

Fig. 2. Serum T_3 concentrations after oral T_3 and thyroglobulin. Four subjects received 75 μg T_3 on one occasion and 5 grains of thyroglobulin (T_3 content 90 μg) on another. Points indicate mean ± SEM.

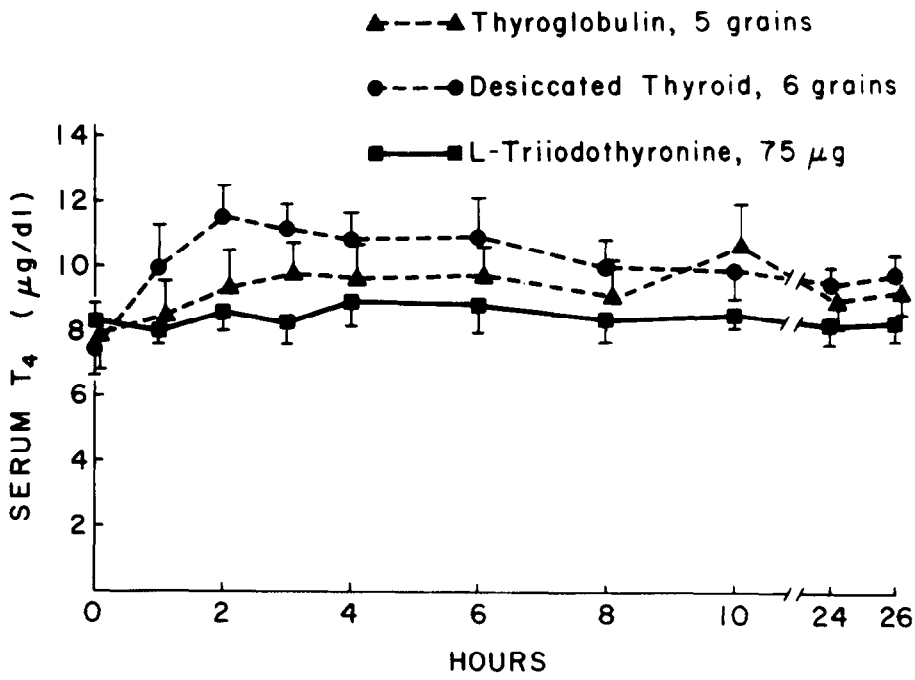

Fig. 3. Serum T_4 concentrations following oral T_3, desiccated thyroid and thyroglobulin in the subjects shown in Figs. 1 and 2. Six subjects received 75 μg T_3, four received 6 grains of desiccated thyroid, and four received 5 grains of thyroglobulin. Points indicate mean + SEM.

ized T_3 charcoal uptake rose from 0.98 to a maximum of 1.05 4h after the dose. The mean peak Free T_3 Index after 75 μg T_3, 500 ± 47 at 4h, was much greater than the mean peak Free T_3 Index after 3 mg T_4, 290 ± 30 at 2 days (Fig. 5).

DISCUSSION

Approximately half of thyroid hormone prescriptions are written for animal-derived thyroid preparations which contain both T_3 and T_4. Recent studies have indicated that the quantity of T_3 and T_4 in such preparations is greater than previously estimated, that there exists variability in hormone content in various preparations from different manufacturers, and that the United States Pharmacopeia's standard, that thyroid tablets contain 0.17–0.23% iodine by weight, provides no guarantee of the T_3 or T_4 content of these preparations.[1,2] The current study was undertaken to explore methods for determining the bioavailability of thyroid hormones in these preparations since this could vary independently of hormone content.

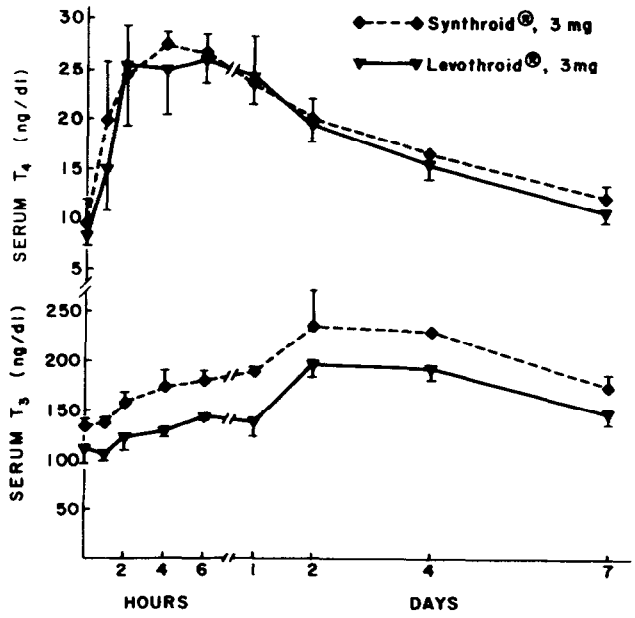

Fig. 4. Serum T_4 and T_3 concentrations after oral T_4. Three subjects received 3 mg of Levothroid® on one occasion and 3 mg of Synthroid® on another. Points indicate mean ± SEM.

Several investigations have indicated that the serum T_3 concentration increases rapidly after ingestion of thyroid USP.[8,9] Since T_3 must presumably be released from the thyroglobulin molecule in the gut prior to absorption, it seemed plausible that serum T_3 levels achieved following administration of desiccated thyroid or thyroglobulin might differ from those observed after administration of synthetic T_3. This did not prove to be the case: there were no significant differences among synthetic T_3, desiccated thyroid and thyroglobulin in the integrated T_3 absorption per μg T_3 in the tablets or in the time to the peak serum T3. Since synthetic T_3 is almost completely absorbed,[10] the T_3 in

Table 2. Integrated Serum T_4 and T_3 Increments Over 48 hr Following Oral T_4

	Integrated Serum T_4 Increment	Integrated Serum T_3 Increment
Dose	(μg · hr/dl)	(ng · hr/dl)
A 3 mg Levothroid®	720 ± 110	3,100 ± 1,100
B 3 mg Synthroid®	670 ± 50	3,840 ± 1,370

Results are mean ± SEM.

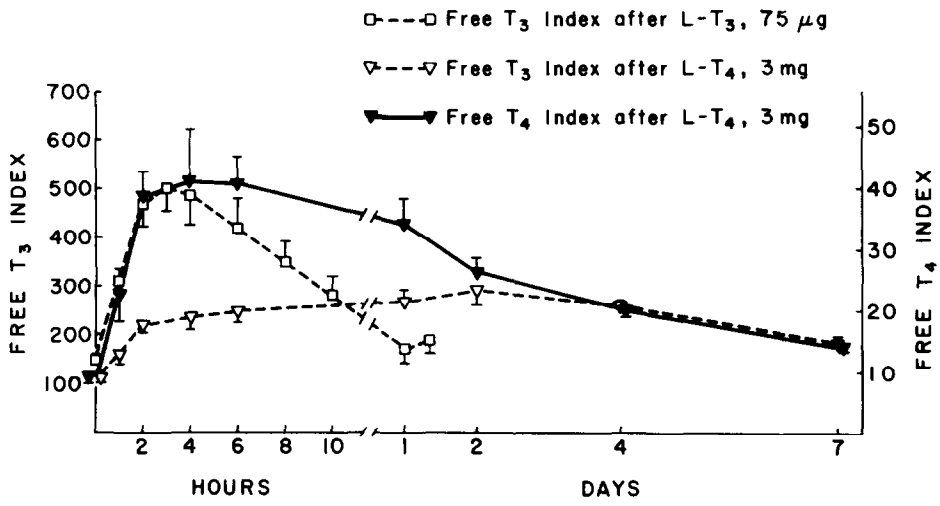

Fig. 5. Free T_4 Index and Free T_3 Index measurements. Six subjects received 75 μg T_3 orally. Three subjects received 3 mg T_4 orally twice (Synthroid® once and Levothroid® once); data from all six T_4 absorption studies are pooled. Points indicate mean ± SEM.

desiccated thyroid or thyroglobulin tablets may be regarded as virtually entirely bioavailable. Since the serum T_4 also increases modestly after both thyroglobulin and desiccated thyroid, the T_3 derived in vivo from T_4 could contribute to the increase in serum T_3 in the first day after the administration of these compounds. This contribution is likely to be small, however, given the relatively small quantities of T_4 present in the thyroid preparations, 363 or 275 μg[1] and the minimal increases in T_3 observed in the first 24 hr after 3 mg of T_4 (Fig. 5). Conversely, suppression of endogenous T_4 and T_3 production is also unlikely to be a quantitatively important factor in the T_3 absorption curves, given the absence of detectable change in serum T_4 after synthetic T_3 ingestion (Fig. 3).

This conclusion leaves two possible explanations for the apparent discrepancy between the hormone content of the tablets and the biological potency ratio of desiccated thyroid to T_4, as determined by Sawin, et al.[5] First, there could be impaired bioavailability of T_4 from desiccated thyroid tablets. This seems unlikely, given the apparent high degree of T_3 bioavailability in these tablets, and the prompt increment in serum T_4 after desiccated thyroid and thyroglobulin (Fig. 3). However, the increase in serum T_4, while significant, is too small to allow firm conclusions regarding T_4 bioavailability, and the potential toxicity of the T_3, which would accompany the requisite quantities of T_4 given as desiccated thyroid, preclude definitive experimental verification of this assumption. A second, and in our opinion more likely, explanation is that the use of basal and TRH-stimulated serum TSH concentrations as a biological assay for thyroid hormones would give more weight to T_4 than to "metabolically equivalent" combinations of T_4 and T_3. That is, a TSH based bioassay may overlook much of the potency of T_3 in terms of classic thyroid hormone actions such as calorigenesis. This would be predicted from recent animal studies demonstrating that pituitary TSH secretion is determined by both serum T_3 and serum T_4, via intrapituitary T_4 to T_3 conversion, whereas tissue such as liver, kidney and heart, important for calorigenic effects of T_3, depend predominantly on the plasma T3 concentrations for intracellular T_3.[11]

Testing the pituitary-thyroid axis by the use of a single 3 mg T_4 dose is an attrative alternative to the T_3 suppression test (75 μg T_3/day for 8 days), because of the ease of administering a single T_4 dose, the absence of manifestations of thyrotoxicosis, and the comparable degree of thyroid suppression attained in normals.[12,13] In the present study impressive peak serum T_4 levels of about 27 μg/dl were achieved between 4–6 hr after 3 mg T_4. At the same time, there were substantial increases in the free fraction of T_4 measured by the normalized charcoal T_3 uptake, and a consequent five-fold increase of the free T_4 index. In agreement with previous observations,[12,13] none of the subjects experienced hypermetabolic symptoms after 3 mg T_4. This can perhaps be explained by the modest change in the free T_3 index. Consistent with previous observations, the peak serum T_3 occurred at 2–4 days following 3 mg of T_4.[13] The small increment of serum T_3 at 4–6 hr after T_4 administration could arise from conversion of T_4 to T_3 in the gastrointestinal tract or may represent a small amount of T_3 contaminating the T_4 tablets. We found such contamination to be 2% or less.[1,2]

Following submission of this manuscript, Valente et al.[14] reported a peak T_3 increment of about 35 ng/dl 4h after ingestion of 1 mg T_4 in 4 hypothyroid subjects. This was attributed to 0.8% contamination of the T_4 preparation (synthroid) with T_3 as measured by RIA. We found a mean T_3 increment of about 47ng T_3/dl 6 hr after 3 mg of T_4. The more modest increase per mg thyroxine we observed is partly due to the fewer available TBG binding sites in our subjects, due to the

marked increase in serum T_4. In addition, other differences in the absorption, distribution and metabolic clearance of T_3 between euthyroid and hypothyroid subjects and differences in the T_3 contamination in the T_4 preparations must be considered in comparing the two studies.

T_4 to T_3 conversion accounts for approximately 43% of T_4 metabolism.[15] It is, however, not possible to analyze T_4 to T_3 conversion after T_4 administration in this study, because of the marked changes in the free T_4 and T_3 fractions and in the volumes of distribution. Nonetheless, the integrated T_3 concentration data after T_4 ingestion (Table 2) show that Levothroid and Synthroid, at equal doses, provided similar amounts of substrate for extrathyroidal T_3 production. The integrated T_4 absorption figures for Synthroid and Levothroid were likewise comparable. Thus, unlike Jacobson et al.,[6] we found that Levothroid and Synthroid are generic equivalents, despite the fact the Levothroid tablets disintegrate much more rapidly in water than Synthroid tablets. Others have also found these two preparations to be equivalent.[16,17]

The present results show that measurements of serum T_4 and T_3 concentrations shortly after ingestion of thyroid hormone replacement preparations provide useful information about thyroid hormone bioavailability. For T_3, bioavailability appears to be very similar for the two Thyroid, USP preparations and synthetic T_3 tablets. This technique could be used to assess bioavailability of thyroid hormones in generic brands of Thyroid, USP or synthetic T_4 or T_3. It could also be employed to evaluate thyroid hormone absorption in patients suspected of malabsorption.

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