from these investigations is that the use of sodium chloride as an isotonic agent with thimerosal as preservative in ophthalmic preparations is open to question.

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Bioavailability of Propylthiouracil in Humans

H. P. RINGHAND *, W. A. RITSCHEL *x, M. C. MEYER ‡, A. B. STRAUGHN ‡, and B. E. CABANA §

Received April 4, 1982, from the **College of Pharmacy, University of Cincinnati Medical Center, Cincinnati, OH 45267,* ‡*Department of Pharmaceutics, College of Pharmacy, University of Tennessee, Memphis, TN 38163,* and the §*Food and Drug Administration, Division of Biopharmaceutics, Rockville, MD 20852.* Accepted for publication October 6, 1982.

Abstract □ Single lots of five commercially available 50-mg propylthiouracil formulations were evaluated *in vitro* and *in vivo*. Each product met the USP XIX specifications for drug content, content uniformity, and disintegration time. However, major differences were noted among products in their rate and extent of dissolution. Statistically significant differences ($p < 0.05$) were observed *in vivo* among the drug formulations at all but one of the sampling times, as determined from crossover blood level studies in 12 healthy male volunteers. The differences among the areas under the plasma level–time curves for the various products were not statistically significant. No statistically significant correlations were found between the *in vitro* and *in vivo* parameters studied.

Keyphrases □ Propylthiouracil—human plasma levels *in vivo*, bioavailability, correlation with *in vitro* dissolution □ Bioavailability—propylthiouracil, human plasma, correlation with *in vitro* dissolution □ Dissolution, *in vitro*—propylthiouracil, correlation with *in vivo* bioavailability, humans

Propylthiouracil, a thyrostatic drug that inhibits the synthesis of hormones within the thyroid gland and reduces the conversion of thyroxine (T_4) to the more potent triiodothyronine, T_3, in the peripheral tissues (1), is prescribed for the chronic treatment of hyperthyroidism and the preparation of hyperthyroid patients for surgery. While differences in bioavailability among propylthiouracil formulations have not been documented, propylthiouracil has been included in several lists of drugs with potential or actual differences in bioavailability (2, 3). The present study involved a crossover comparison to assess the relative bioavailability of five currently marketed products.

EXPERIMENTAL

Product Selection—Five single lots of 50-mg propylthiouracil tablets from separate manufacturers were evaluated; the individual products are identified in Table I. The sixth formulation, a solution of propylthiouracil, was utilized as a reference and was prepared as follows.

A stock solution of sucrose–glycerin was prepared by combining 6.5 g of sucrose with 12.5 ml of glycerin, diluting to 500 ml with distilled water. The day before each study a sucrose–glycerin–citric acid solution was prepared by adding 2.0 ml of 0.5 *M* citric acid to 95.4 ml of the sucrose–glycerin stock solution. On the day of each study the propylthiouracil reference solution was freshly prepared using USP propylthiouracil powder[1]. A 150-mg quantity of the powdered propylthiouracil was accurately weighed and dissolved in 6 ml of 0.2 *M* NaOH. The resulting solution was then diluted immediately with 24 ml of the sucrose–glycerin–citric acid solution and administered to the subject.

Clinical Study Protocol—Twelve male volunteers[2] underwent urinalysis and hematological and blood chemistry[3] testing to ensure that they were in good health. Also included in the initial medical evaluation was a T_4 determination by radioimmunoassay, T_3 uptake, and free thyroxine blood study. As a precaution against possible side effects of the propylthiouracil, the white blood cell and differential count, as well as prothrombin time, were monitored at the midpoint of the 6-week study. The subjects ranged in age from 20 to 25 years, in height from 172 to 198 cm, and in weight from 72 to 93 kg; all were considered to be of normal weight for their height (4).

The sequence of dose administration was based on a crossover matrix, designed to minimize the influence of any residual or cumulative effects of the preceding doses (5). Each subject received three 50-mg tablets or reference solution equivalent to 150 mg of propylthiouracil once a week for 6 weeks. The propylthiouracil formulations were administered with 200 ml of water in the morning following an overnight fast[4]. No food and water were permitted for 4 hr after ingestion of the dose. The subjects were instructed to avoid any food high in fat content on days of testing to minimize analytical problems associated with excessive lipids in the plasma. While the subjects were not sequestered on the days of testing they were instructed to avoid undue exercise. Subjects were also cautioned to avoid any other medication during the 6-week period of the study.

[1] USP propylthiouracil powder was provided by Lederle Labs.

[2] Staff and students of the University of Tennessee Center for the Health Sciences. Written informed consent was obtained.

[3] SMA 18/90.

[4] A standardized meal was not required prior to fasting.

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Table I—*In Vitro* Test Results for 50-mg Propylthiouracil Products [a]

Product	Assay, % of Label Claim	Content Uniformity, Mean % of Label Claim (*SD*)[b]	Dissolution Profile, Mean % of Label Claim (*SD*)[c] 0.1 *N* HCl 5 min	0.1 *N* HCl 20 min	0.1 *N* HCl 60 min	Water 5 min	Water 20 min	Water 60 min
1	—	—	—	—	—	—	—	—
2	102.0	104.0 (1.0)	2.5 (0.2)	8.7 (0.5)	20.6 (1.0)	3.0 (0.3)	10.0 (1.1)	24.6 (2.0)
3	101.0	102.0 (1.5)	3.3 (0.8)	12.5 (0.6)	27.4 (0.6)	3.2 (0.7)	10.0 (0.9)	21.3 (1.9)
4	99.8	104.0 (1.6)	50.3 (12.5)	77.3 (12.4)	88.3 (11.0)	57.7 (9.6)	86.8 (10.1)	94.2 (8.1)
5	102.0	102.0 (1.6)	25.8 (3.2)	87.8 (5.5)	102.1 (2.7)	26.2 (5.4)	54.4 (9.7)	80.8 (10.2)
6	100.0	99.8 (2.5)	4.6 (0.9)	21.3 (5.6)	53.8 (11.1)	5.3 (1.4)	23.1 (5.3)	58.6 (11.8)

[a] Manufacturer and lot numbers are as follows: (1) propylthiouracil reference solution prepared as described in the text; (2) Eli Lilly, OAF 35B; (3) Lederle, 461-260; (4) Parke-Davis, TB 299; (5) Mylan, 1005410; (6) Richlyn, 29327. All products were obtained from FDA regional offices. [b] Means are based on 10 determinations (*SD*). [c] Means are based on six determinations (*SD*).

Table II—Mean Plasma Levels of Propylthiouracil in 12 Subjects Following Ingestion of a Single 150-mg Dose

Product[a]	Propylthiouracil Plasma Levels at Each Sampling Time, μg/ml 0.33 hr	0.67 hr	1.0 hr	1.5 hr	2.0 hr	3.0 hr	4.0 hr	6.0 hr	8.0 hr
1	3.04 (64.5)[b]	3.94 (20.6)	3.53 (15.7)	2.80 (19.9)	2.27 (23.4)	1.48 (33.1)	0.97 (40.9)	0.42 (80.5)	0.17 (96.9)
2	0.10 (130.0)	0.47 (62.1)	0.86 (44.8)	1.80 (37.9)	2.62 (25.1)	2.55 (22.0)	1.73 (24.4)	0.76 (42.0)	0.31 (52.0)
3	0.82 (146.3)	2.57 (73.2)	2.55 (59.7)	2.54 (38.7)	2.53 (41.3)	2.04 (38.1)	1.51 (60.6)	0.59 (56.1)	0.24 (60.4)
4	1.78 (77.4)	3.29 (42.0)	3.44 (23.6)	3.06 (19.0)	2.48 (18.8)	1.75 (32.7)	1.15 (37.5)	0.49 (40.3)	0.19 (57.6)
5	1.35 (84.1)	2.65 (25.9)	2.95 (20.2)	3.04 (17.1)	2.66 (20.3)	1.86 (25.4)	1.24 (27.8)	0.51 (41.1)	0.21 (43.1)
6	1.13 (92.4)	3.08 (53.2)	3.22 (39.5)	3.14 (25.1)	2.64 (19.5)	1.79 (21.1)	1.20 (35.0)	0.45 (43.7)	0.20 (48.1)

[a] See Table I for product information. [b] Values in parentheses represent the coefficient of variation, *i.e.*, *SD* × 100/mean.

Blood samples (7 ml) were collected in heparinized containers prior to ingestion of the dose and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, and 8 hr post-administration. The blood samples were immediately centrifuged, and the plasma fractions were removed and frozen until assayed. All analyses were completed within 4 days from the time of sampling.

Assay of Plasma Samples—The determination of propylthiouracil concentrations was performed using a high-performance liquid chromatographic (HPLC) method developed by Ringhand and Ritschel (6). A 3.0-ml plasma sample was added to 0.5 g of ammonium sulfate and mixed vigorously for 1 min. The mixture was extracted for 10 min with 15.0 ml of chloroform. After centrifugation, a 10.0-ml aliquot of the chloroform layer was removed and mixed with 1.0 ml of a 1.75-μg/ml methylthiouracil internal standard solution and evaporated to dryness.

The residue was dissolved in 250 ml of mobile solvent, acetic acid–methanol–water (10:75:915), and 25 μl was injected into the chromatograph[5]. The chromatograph was equipped with a fixed-wavelength 280-nm detector and a stainless steel column, 25 cm × 3.1-mm i.d., packed with an octadecylsilane reverse-phase support[6]. A flow rate of 2.3 ml/min was used. Plasma propylthiouracil concentrations were determined from standard curves of propylthiouracil/methylthiouracil peak height ratio *versus* propylthiouracil concentration, prepared over a range of 0.1–5.0 μg/ml using pooled human plasma.

***In Vitro* Tests**—The USP XIX product assay, content uniformity, and tablet disintegration were performed on each product (7). Dissolution profiles were determined for each product on six individual tablets in two different media: water and 0.1 *N* HCl. Tests were performed using the USP Dissolution Apparatus 2 (8) maintained at 50 rpm and a temperature of 37 ± 0.5°[7]. Samples (10 ml) were taken at 5, 20, and 60 min. The liquid level was maintained by adding 10-ml aliquots of dissolution medium to replace the sample aliquots as they were taken.

Statistical Analysis—The relative bioavailability of the five propylthiouracil products was determined using the following parameters:

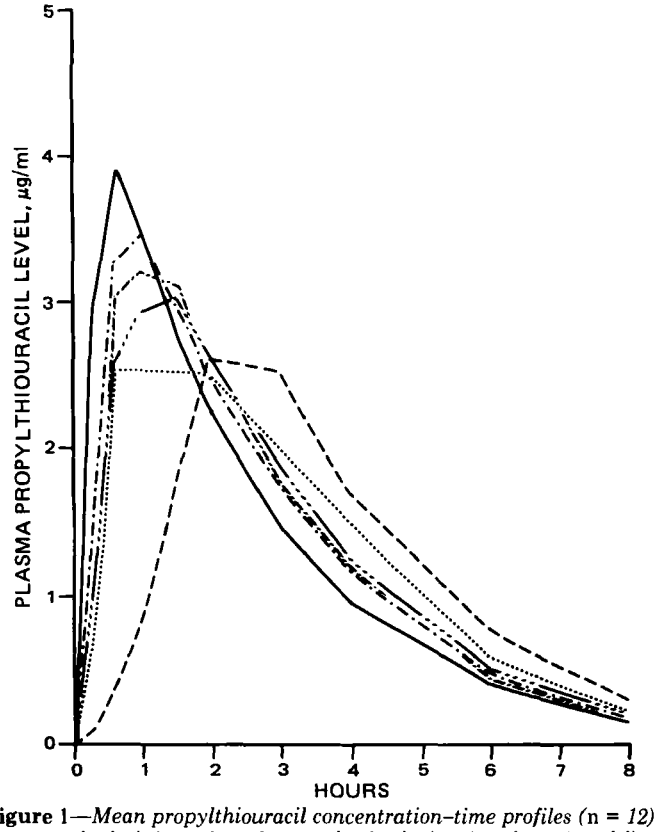

Figure 1—*Mean propylthiouracil concentration–time profiles (n = 12) on peroral administration of a standard solution (product 1) and five different commercially available propylthiouracil tablet preparations (products 2–6). Key: (————) product 1; (— — — — — —) product 2; (·····) product 3; (— · — · — · —) product 4; (▬ ▬ ▬ ▬) product 5; (▬ ▬ ▬ ▬) product 6.*

[5] Model 202/401; Waters Associates, Milford, Mass.
[6] Spherisorb 10 μm; Spectra-Physics, Santa Clara, Calif.
[7] 33710-S1 Body for Reaction Kettle—1000 ml, Kimble Glass Co., Vineland, N.J., was substituted for the dissolution vessel described.

Table III—Significance Levels for Differences Between Subjects, Weeks, and Drugs

Parameter	F Ratio Test (p Value) Subject Groups	Weeks	Drugs
Plasma Concentration			
20 min	0.218	0.814	<0.001
40 min	0.259	0.806	<0.001
1.0 hr	0.238	0.622	<0.001
1.5 hr	0.014	0.676	<0.001
2.0 hr	0.019	0.221	0.304
3.0 hr	0.076	0.009	<0.001
4.0 hr	0.053	0.362	0.001
6.0 hr	0.293	0.672	0.004
8.0 hr	0.272	0.218	0.002
Peak plasma concentration	0.038	0.787	<0.001
Time to peak plasma concentration	0.120	0.724	<0.001
AUC			
0–8 hr	0.072	0.046	0.803
$0 \rightarrow \infty$	0.110	0.031	0.766

Table IV—Newman-Keuls *A Posteriori* Test for Significant Product Differences in Parameters Studied

Parameter	Product Ranking (Lowest to Highest)[a]					
Peak concentration	2	5	3	4	6	1
Time to peak concentration	1	6	4	5	3	2
AUC						
0–8 hr	2	1	6	5	3	4
$0 \rightarrow \infty$	2	1	6	5	4	3
Plasma concentration						
20 min	2	3	6	5	4	1
40 min	2	3	5	6	4	1
1.0 hr	2	3	5	6	4	1
1.5 hr	2	3	1	5	4	6
2.0 hr	1	4	3	2	6	5
3.0 hr	1	4	6	5	3	2
4.0 hr	1	4	6	5	3	2
6.0 hr	1	6	4	5	3	2
8.0 hr	1	4	6	5	3	2

[a] Products underlined by a common line not found to differ significantly ($p > 0.05$). See Table I for product information.

plasma concentrations at each sampling time, time of peak plasma concentration, peak plasma concentration, and area under the plasma concentration–time curve (AUC). A three-way analysis of variance (9) and the Newman-Keuls *a posteriori* test (10) were used to analyze for differences among products, subjects, and weeks.

RESULTS AND DISCUSSION

Table I summarizes the results of the *in vitro* tests. Each of the five products met the USP XIX requirements for drug content, disintegration, and content uniformity. However, major differences were observed for the rate and extent of dissolution of the different drug products[8].

The average plasma concentrations for each product at each sampling time are summarized in Table II and illustrated graphically in Fig. 1. The statistical analyses of differences among subject groups, weeks, and test products at each sampling time are given in Tables III and IV. Significant differences ($p < 0.05$) in plasma levels were observed among the products at all sampling times except at 2 hr. The Newman-Keuls analysis found

[8] USP XIX does not include a dissolution requirement for propylthiouracil tablets.

Table V—Propylthiouracil Bioavailability Parameters[a]

Product[b]	Peak Plasma Concentration, μg/ml	Time to Peak Plasma Concentration, hr	AUC (0–8 hr), μg·hr/ml	AUC ($0 \rightarrow \infty$), μg·hr/ml
1	4.32	0.61	10.84	11.29
	(18.7)	(46.4)	(24.6)	(27.9)
2	2.77	2.50	10.39	11.09
	(18.6)	(20.7)	(17.9)	(18.6)
3	3.83	1.61	11.07	11.71
	(22.6)	(72.5)	(21.5)	(21.8)
4	3.98	1.10	11.16	11.61
	(20.5)	(65.0)	(19.2)	(19.8)
5	3.38	1.15	11.04	11.57
	(15.9)	(43.2)	(17.7)	(18.6)
6	3.98	1.06	11.00	11.38
	(21.9)	(51.2)	(15.0)	(15.7)

[a] Each value represents the mean of 12 subjects. *RSD* (*SD* × 100/mean) is given in parentheses. [b] See Table I for product information.

no significant differences among products 3–6 at any of the sampling times. All observed differences were due to products 1 and 2 being different from one or more of the other dosage forms.

The mean values of peak concentration, time to peak concentration, $AUC_{0-8\ hr}$ and $AUC_{0\rightarrow\infty}$ are summarized in Table V; the statistical analyses of differences among these parameters are given in Tables III and IV. There were no significant differences ($p < 0.05$) among products for either $AUC_{0-8\ hr}$ or $AUC_{0\rightarrow\infty}$. The ranges for both AUC values represented a difference of <7%.

The mean time (0.6 hr) for product 1, the reference solution, to reach peak concentration was significantly different from the 2.5 and 1.6 hr required to reach peak concentration for products 2 and 3, respectively. The mean time to reach peak concentration was significantly longer for product 2 than for all other products.

Since the products exhibited equal AUC values, products demonstrating the longest times to reach peak concentration would be expected to have lower peak concentrations. This was observed as product 1, the product exhibiting the shortest time to peak concentration had the greatest peak plasma concentration (4.23 μg/ml). In addition, product 2 (which demonstrated the longest time to peak concentration) had the lowest peak concentration (2.77 μg/ml).

It is evident that product 2 exhibited a significantly slower rate of absorption than the other four tablet products (products 3–6). As a result product 2 cannot be considered to be bioequivalent to those dosage forms. The clinical significance of this apparent slower absorption of product 2, or conversely the more rapid absorption of products 3–6, is not known.

To substantiate the ability of the study to detect significant differences among the parameters, a power analysis was applied to the data (Table VI). Because of the large variability obtained for the plasma levels of propylthiouracil at each sampling time, a subject population in excess of 30 would have been required for a 20% difference to be significant (p

Table VI—Power Analysis[a]

Parameter	Minimum Number of Subjects for 20% Differences	Minimum Detectable Difference, %
Plasma concentration		
20 min	>30	55.5
40 min	>30	41.8
1.0 hr	>30	41.1
1.5 hr	>30	34.4
2.0 hr	16–19	25.9
3.0 hr	10–11	18.6
4.0 hr	>30	35.6
6.0 hr	>30	41.2
8.0 hr	>30	39.1
Peak plasma concentration	16–19	23.7
Time to peak plasma concentration	>30	40.8
AUC		
0–8 hr	6–7	14.0
$0 \rightarrow \infty$	6–7	14.5

[a] $\alpha = 0.05$, $\beta = 0.2$.

< 0.05) at all but two of the sampling times. Nevertheless, significant differences were observed since actual differences exceeded 20%.

The relative standard deviation for the mean peak plasma concentration was <25%, and the number of subjects necessary to detect a 20% difference was 16–17. Statistically significant differences were observed for this parameter, since actual differences were >50%. Similarly, it would have taken >30 subjects to detect a 20% difference in time to reach peak plasma concentration. However, significant differences were observed because actual differences exceeded 200%. No significant differences were seen among the products for $AUC_{0-8\ hr}$ or $AUC_{0\to\infty}$, although the power of the study was adequate to detect differences of 14.5%.

There was a perfect rank-order correlation of the mean percent of drug dissolved at 5 min in both acid and water for products 2–6 and the propylthiouracil plasma concentration observed at 20 min. The best correlations were found between the mean percent dissolved in water at 5, 20, and 60 min and the plasma propylthiouracil concentration at 20 min, with correlation coefficients of 0.81, 0.86, and 0.89, respectively. Corresponding correlation coefficients of 0.82, 0.80, and 0.85 were found for dissolution data obtained in acid. Attempts to relate either peak plasma propylthiouracil concentration or time to peak concentration were less successful. Correlation coefficients describing peak concentration and any of the dissolution values were all <0.42. The best correlation with time to peak concentration was with the percent dissolved at 60 min in either water or acid ($r = 0.75$). It is apparent the results of the dissolution studies were not useful in providing generally applicable correlations with *in vivo* data. However product 2, which exhibited the longest time to achieve peak concentration, was somewhat more slowly dissolved in acid at each sampling time compared with the other more rapidly absorbed dosage forms.

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Pharmacokinetic Profile of Intravenous Liposomal Triamcinolone Acetonide in the Rabbit

ISAAC ABRAHAM ˣ, JANE C. HILCHIE, and MICHAEL MEZEI

Received June 15, 1981, from the *College of Pharmacy, Dalhousie University, Halifax, Nova Scotia, Canada.* Accepted for publication October 8, 1982.

Abstract □ The pharmacokinetics of triamcinolone[2-^{14}C]acetonide, encapsulated in neutral multilamellar liposomes, and a control preparation of the steroid in a 3:1 solution of polyethylene glycol–water was investigated in the rabbit after single intravenous bolus injections. Blood samples were obtained at various times up to 7 hr postinjection and assayed for the drug by liquid scintillation counting. Blood drug concentration–time data showed biexponential decay and were analyzed by nonlinear, least-squares regression analysis to obtain the initial (time zero) drug concentration $[(C_b)_0]$ and the initial (fast, α) and terminal (slow, β) disposition rate constants. From these estimates the central compartment volume (V_c) and the respective half-lives $[(t_{1/2})_\alpha, (t_{1/2})_\beta]$ of the fast and slow disposition phases were calculated. The total body clearance (CL_T) and the apparent distribution volume (Vd) were obtained by nonparametric analysis. Significant differences were observed between the liposome-encapsulated dosage form and the solution of the steroid in β and Vd_β. While β for the liposomal form was smaller than that for the solution, the apparent Vd was larger with the liposome-encapsulated drug. There was no difference in the total body clearance of the drug in the two dosage forms. Results of the study suggest that when administered by the intravenous route, liposome-encapsulated drug may exhibit extensive tissue distribution and a prolonged half-life.

Keyphrases □ Triamcinolone acetonide—liposomal encapsulation, pharmacokinetics, rabbits □ Dosage forms—liposomal encapsulation, triamcinolone acetonide, pharmacokinetics, rabbits □ Pharmacokinetics—liposome-encapsulated triamcinolone acetonide, rabbits

In recent years liposomes—artificial phospholipid vesicles—have gained increasing attention as a potential drug delivery system (1). A common objective for the choice of liposomes as drug carriers is the desire to ensure selective distribution or localization of therapeutic agents in specific organ tissues (2–4). By this means, high concentrations of an agent in an organ of interest can be attained while reducing potential toxicity to other organs, which can result from indiscriminate dispersion of the agent in the body. Notable successes have been reported with liposomal preparations in the treatment of arthritic joints (3, 5) and experimental leishmaniasis (6) and in the alleviation of respiratory distress syndrome in infants (7). However, reports on the formal pharmacokinetic analyses of liposome-encapsulated drugs are rather scanty.

Unlike many drug delivery systems that are designed to release the active component (drug) instantly *in vivo*, the liposome-encapsulated dosage form in circulation may remain as a single phospholipid vesicle for relatively long periods. In this instance the pharmacokinetic behavior of the encapsulated drug will largely be determined by the disposition characteristics of the liposomal entity. Several physical and chemical factors of the liposome can, therefore, potentially influence the disposition of liposome-entrapped drug. Such factors include vesicle size, surface charge, and lipid composition.

As interest in the clinical application of liposomes as drug carriers grows, there is need to gain more information about the pharmacokinetics of drugs and, hence, their

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