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CORRELATION BETWEEN ANTITHYROID EFFECT AND SERUM CONCENTRATIONS OF PROPYLTHIOURACIL IN PATIENTS WITH HYPERTHYROIDISM

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1 Correlation between the kinetics of propylthiouracil and its antithyroid effect was studied in 17 hyperthyroid patients. The serum concentration of propylthiouracil 1 h after an oral dose of 400 mg of the drug was used as kinetic parameter as this concentration from the previous study was found to correlate significantly ($r = 0.84$, $P < 0.01$) with the area under the serum concentration-time curve.

2 After 3 weeks of treatment with 200 mg propylthiouracil three times daily the serum concentration of propylthiouracil was correlated to the decrease in various thyroid parameters such as total and free indexes of serum thyroxine, triiodothyronine and reverse triiodothyronine.

3 Significant correlations were found between the serum concentration of propylthiouracil and all the measured thyroid variables except reverse triiodothyronine. The highest degree of correlation was obtained between serum propylthiouracil and the percentage decrease in total and free indexes of triiodothyronine ($r = 0.63$ and 0.70, respectively, $P < 0.01$).

4 It is suggested that a serum concentration of propylthiouracil above 4 to 5 μg/ml 1 h after an oral dose of 400 mg of the drug will secure a sufficient and rapid antithyroid effect during continuous therapy.

Introduction

The pharmacokinetics of propylthiouracil (PTU) in humans has recently been investigated in several studies (Schuppan *et al.*, 1973; Kampmann & Skovsted, 1974; McMurray *et al.*, 1975; Sitar & Hunninghake, 1975). PTU is rapidly and almost completely absorbed after oral administration and cleared from the body with a terminal half-life in serum of about 1 h. No significant differences in these kinetic parameters were found between euthyroid and hyperthyroid subjects (Schuppan *et al.*, 1973; Kampmann & Skovsted, 1975; McMurray *et al.*, 1975).

Laboratory, animal and human experiments have provided evidence that PTU is concentrated in the thyroid gland (Marchant *et al.*, 1972; Lazarus *et al.*, 1975; Pharmakiotis & Alexander, 1975; Aungst, Vesell & Shapiro, 1979) exerting its effect on the intrathyroidal hormone metabolism in time exceeding that in which measurable serum concentrations of PTU can be demonstrated. These studies are in agreement with the clinical observation that many hyperthyroid patients can be treated sufficiently with one to two daily doses of PTU (Barnes & Bledsoe, 1972; Greer, Meihoff & Studer, 1965). Although the exact mechanism of action of the antithyroid drugs in the thyroid gland is not definitively established, it has been shown that the effect is closely connected to the intrathyroidal metabolism of the drug itself (Taurog, 1976; Nakashima, Taurog & Riesco, 1978). In contrast to this mechanism no evidence has accumulated concerning the molecular way in which PTU acts outside the thyroid gland, although the microsomal fraction of the liver is supposed to be the main target of action (Visser *et al.*, 1975; Höffken *et al.*, 1976; Chopra, 1977; Chopra *et al.*, 1978). It has been shown in both animal and human studies that the majority of PTU is excreted as a glucuronic acid conjugate, a process which predominantly occurs in the liver (Lazarus *et al.*, 1975; Marchant, Lees & Alexander, 1979).

The purpose of the present study has been to investigate whether any relationship exists between the serum concentration of PTU and its effect on the

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serum concentrations of T_4, T_3 and rT_3 in patients with hyperthyroidism.

Methods

Seventeen hyperthyroid patients were studied, thirteen females aged 28 to 71 years and four males aged 44 to 70 years. The mean age (± s.d.) of all the subjects was 53 ± 15 years. The weight varied from 53 to 93 kg with a mean of 63.7 ± 12.0 kg and the height varied from 1.54 to 1.80 m. None of the patients had increased values of serum creatinine or any signs of overt untreated clinical ailments apart from the thyrotoxicosis. Informed consent was obtained from all the patients prior to the study after careful explanation of the risks and inconveniences to be expected.

Thirteen of the patients had diffuse goitres, three a nodular goitre, while one patient did not have any enlargement of the thyroid gland. Nine of the 13 goitrous patients had goitres of small to moderate size, while four patients had goitres of very large size. The diagnosis of thyrotoxicosis was established by clinical examination and by measuring the concentration of T_4, T_3 and the T_3-resin test. All the patients had elevated serum T_3 values before treatment while one patient had a normal value of T_4 and was thus regarded as having T_3-thyrotoxicosis. Two of the patients received other kind of medicine than propylthiouracil. One patient was treated with digoxin and bumetanide, while another patient for a long period received a small constant dose of metoprolol.

The patients were all treated with 200 mg of PTU three times daily with an interval of approximately 8 h. The concentration of T_4, T_3, rT_3 and T_3-resin test was measured before and after 3 weeks of treatment. There were no drop-outs and no adverse reactions during the study.

The serum concentraiton of PTU was measured at the beginning of the study from a blood sample collected exactly 1 h after supervised oral administration of 400 mg of the drug. The serum concentration of PTU was determined spectrophotometrically according to the method of Ratliff, Gilliland & Hall (1972). The precision of the method has been published in a previous paper (Kampmann & Skovsted, 1974). The intraassay coeffficient of variation of the PTU determination was up to 5%, while the interassay coefficient of variation was up to 8%. The optical density of the blank was below 0.02 in each case. All PTU and hormone concentrations are expressed as the mean of two analyses performed on different days. Hormone concentrations from one patient before and after treatment with PTU were analysed in the same analytical run.

Serum T_4 was determined by a modification of the Murphy method (Siersbaek-Nielsen, 1967), serum T_3 and rT_3 by radioimmunoassays (Skovsted, 1979). rT_3 was corrected for T_4-cross reactions (about 0.2%). Free T_4 index (FT_4-I), free T_3 index (FT_3-I) and free rT_3 index (FrT_3-I) were calculated as total hormone concentration multiplied by the triiodothyronine test and given in arbitrary units (Hansen, 1964).

Normal limits (mean ± 2 s.d.) for total T_4 concentrations in our laboratory are 4.3–10.0 μg/ml; for T_3 106–182 ng/100 ml; for corrected rT_3 9–31 ng/100 ml and for T_3-resin test 0.8–1.2.

For statistical purposes Student's *t*-test for paired and non-paired comparisons and linear regression analysis were used.

Results

The effect of treatment for 3 weeks with 200 mg PTU three times daily on the thyroid hormones are given in Table 1. All measured and calculated variables decreased significantly ($P < 0.01$) during this period. The percentage decrease of T_4 is equal to the percentage decrease of serum T_3. The decrement in FT_4-I and FT_3-I was similar but due to a concomittant decrease in the T_3-resin test significantly ($0.001 < P < 0.01$) larger than the decrease in the total hormone concentration. After treatment with PTU 11 of the 16 patients with increased pre-treatment values of T_4 showed T_4 values in the upper normal concentration range, while the concentration of T_3 was above the

Table 1 Thyroid parameters (mean ± s.d.) before and after 3 weeks of treatment with 600 mg propylthiouracil to 17 patients with hyperthyroidism. *r* values denote the correlation between the serum concentration of propylthiouracil and the percentage decrease of the different variables.

	Before treatment	*After treatment*	*Decrease (%)*	r	*Significance*
Serum thyroxine (μg/100 ml)	14.6 ± 2.8	8.3 ± 3.5	44 ± 18	0.55	$0.02 < P < 0.05$
Serum triiodothyronine (ng/100 ml)	420 ± 138	217 ± 89	47 ± 15	0.63	$0.001 < P < 0.01$
Free thyroxine index (units)	22.7 ± 7.0	8.8 ± 5.8	61 ± 19	0.53	$0.02 < P < 0.05$
Free triiodothyronine index (units)	655 ± 269	222 ± 123	64 ± 14	0.70	$0.001 < P < 0.01$
Triiodothyronine test (units)	1.52 ± 0.26	0.99 ± 0.24	34 ± 15	0.50	$0.02 < P < 0.05$
Serum reverse triiodothyronine (ng/100 ml)	67.4 ± 29.2	31.8 ± 14.1	47 ± 24	0.45	$0.05 < P < 0.10$

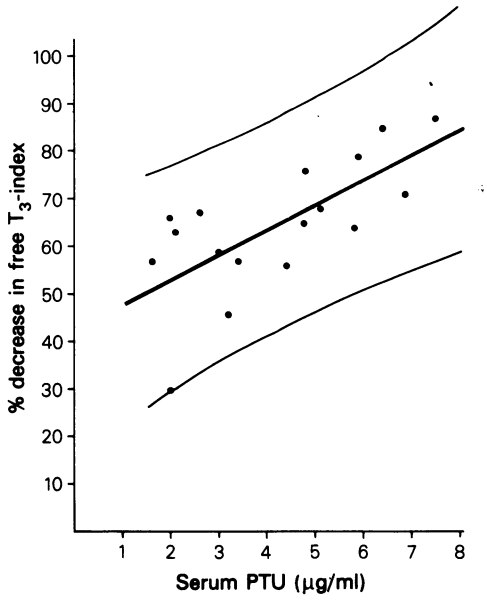

Figure 1 Correleation (r = 0.70; $P < 0.01$) between percentage decrease in free T_3-index after 3 weeks of treatment with 200 mg propylthiouracil (PTU) three times a day and the serum concentration of PTU measured 1 h after oral administration of 400 mg PTU. The curved lines indicate the 95% confidence limits of the individual values of free T_3-index.

upper normal limit in most of the patients as only seven patients were in the euthyroid concentration range. Patients with large diffuse or nodular goitres showed no remarkable differences from the total population.

The serum concentration of PTU ranged from 1.6 μg/ml to 7.5 μg/ml with a mean value of 4.2 ± 1.9 μg/ml (mean ± s.d.).

Table 1 also shows the correlation between the serum concentration of PTU and the percentage decrease in the various measured and calculated variables. Significant correlations were found between the serum concentration of PTU and all the measured parameters except rT_3. The highest degree of correlation was obtained between serum PTU and FT_3-I and T_3, respectively, while the lowest correlation was found between serum PTU and FT_4-I and T_4, respectively. No significant differences were found among any of the coefficients of correlation.

Figure 1 shows the correlation between the serum PTU and the percentage decrease in FT_3-I. The figure includes the 95%-confidence limits for the individual values of FT_3-I for different serum concentrations of PTU.

Discussion

The present study has demonstrated a significant correlation between the serum concentration of PTU and the percentage decrease in the serum concentration of thyroid hormones after 3 weeks of treatment with 600 mg PTU daily. The highest degree of correlation was found between PTU and the free index of T_3 while the correlation to T_4 and the free index of T_4 was lower.

The concentration of PTU was measured exactly 1 h after oral administration of 400 mg of the drug. It is conceivable that a higher correlation could be obtained using a more reliable kinetic parameter, e.g. the area under the complete serum-concentration-time curve (AUC), which is an integrated expression of the average amount of PTU in the body. Practical considerations, however, made it not feasible to use this method which also in routine clinical practice is inaccessible. Before deciding to use the drug concentration one hour after oral administration as a kinetic parameter it was studied if any relationship existed between AUC and the serum concentration. Data analysis from a previous study (Kampmann & Skovsted, 1975) comprising ten hyperthyroid patients showed a significant correlation of $r = 0.84$ between these two parameters (Figure 2).

A large part of T_3 and the majority of rT_3 is produced by an extrathyroidal monodeiodination of T_4 (Cavalieri *et al.*, 1977; Chopra, 1977; Westgren *et al.*, 1977; Chopra *et al.*, 1978). Several *in vitro*, animal and human experimental studies have provided evidence that PTU in addition to an intrathyroidal effect on hormone production also inhibits the extrathyroidal conversion of T_4 to T_3 and of rT_3 to T_2 (3,3'-diiodothyronine) thus acutely increasing the serum concentration of rT_3 and reducing the concentration of T_3 (Oppenheimer, Schwartz & Surks, 1972; Saberi, Sterling & Utiger, 1975; Westgren *et al.*, 1977; Laurberg & Weeke, 1978; Siersbaek-Nielsen *et al.*, 1978). These alterations can be explained by an effect of PTU on the 5'-deiodinase of the liver (Kaplan, Schimmel & Utiger, 1977; Schimmel & Utiger, 1977). Despite the acute increase in serum rT_3 by PTU, the long term effect is a reduction due to a pronounced decrease in the production of the thyroxine precursor.

In this way PTU seems to have an action upon the kinetics of T_3 in several ways contrasting to a single effect upon the concentration of T_4. This might explain the higher correlation between the kinetics of PTU and T_3 derived parameters relative to those of T_4. PTU is actively concentrated in the thyroid gland by a dose-dependent mechanism and exerting its effect lasting more than 8 h (Barnes & Bledsoe, 1972; Marchant *et al.*, 1972; Lazarus *et al.*, 1975; Pharmakiotis & Alexander, 1975; Aungst *et al.*,

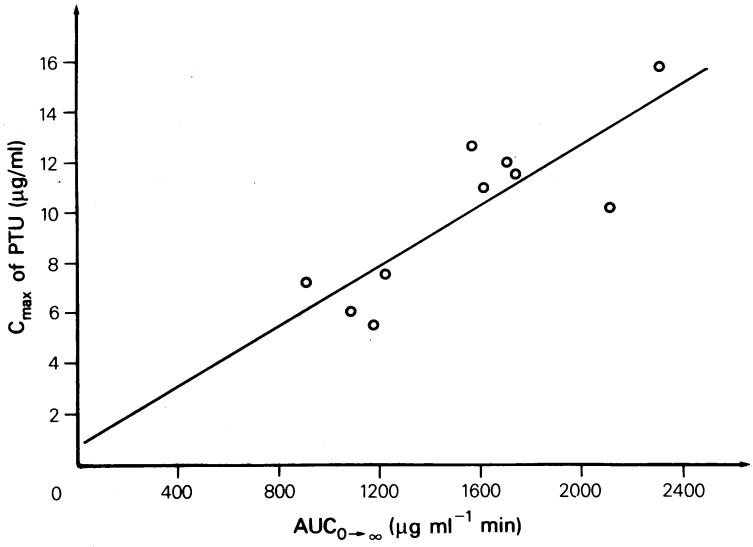

Figure 2 Correlation ($r = 0.84$; $P < 0.01$) between the maximal 1 h serum concentration of propylthiouracil (PTU) and the area under the complete serum concentration-time curve after oral administration of 400 mg PTU to 10 hyperthyroid patients. Data analysis from a previous study by Kampmann & Skovsted (1975).

1979). The extrathyroidal conversion from T_4 to T_3 is supposed to occur mainly in the liver, and the liver tissue might be in more close equilibrium with the PTU in serum compared to the amount of drug in the thyroid gland contributing to a better correlation to the level of T_3 than to that of T_4. The insignificant correlation between serum PTU and rT_3 could be explained by the opposite dual effect of PTU on the concentration of rT_3.

The correlation between PTU and the relative changes in thyroid parameters is in fact a clinical dose-response curve between the concentration and the pharmacological effect of an antithyroid drug. No such curve has been presented previously in humans, although *in vitro* studies have demonstrated a relationship between the amount of an antithyroid compound added to the test tube and the inhibitory effect on a system of thyroid tissue and the necessary enzymes (Taurog, 1976; Nakashima *et al.*, 1978; Melander *et al.*, 1980). A recent study in rats has suggested that a serum concentration of PTU from 0.09 to 0.18 μg/ml blocks thyroid hormone production for up to 6 h (Francis & Rennert, 1980). It has also been shown that increasing doses to hyperthyroid patients resulted in increased T_4/T_3 ratios caused by a relatively more pronounced decrease in the T_3 production (Abuid & Larsen, 1974).

Most pharmacological dose-response curves are of the sigmoidal type often presented as almost straight lines in a logarithmic dose or concentration plot. The calculated *r*-values in the present study have been derived assuming a linear relationship between the measured parameters. Other kind of functions were also investigated and the second highest degree of correlation was obtained after a logarithmic transformation of the serum concentrations resulting in a *r*-value of 0.66 between serum PTU and FT_3-I. The correct relationship cannot be expected to be found from the present study as this would require more data on a wider range of serum concentrations in both the lower and higher concentration range. This is not ethically justified in patients suffering from severe thyrotoxicosis.

From a clinical point of view it seems as serum concentrations of PTU above 4 to 5 μg/ml 1 h after an oral dose of 400 mg of PTU will secure a sufficient and rapid antithyroid effect if the treatment is continued. This concentration is around the value corresponding to the mean percentage decrease in the triiodothyronine index among the patients studied. If substantiated by more extensive studies measurements of serum concentrations of PTU after a single oral dose could be an example of the one point method for estimating dosage requirements for individual patients (Slattery, Gibaldi, & Koup, 1980). Measurements of serum PTU is in particular recommended if a patient otherwise susceptible to antithyroid treatment does not respond properly. The effect of therapy with PTU depends, however, not only upon the amount of PTU in the tissues but also on the

iodine content of the thyroid gland, its size and consistency. Furthermore, the elimination of PTU varies at least with a factor two among hyperthyroidal subjects (Kampmann & Skovsted, 1975). Only the kinetic variation has been examined in this study and a more detailed understanding of all the remaining factors might improve the correlation between the serum concentration of an antithyroid agent and its biochemical and clinical effect.

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