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In-vivo Evaluation in Man of a Hydrophilic Matrix Containing Propylthiouracil

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Abstract

To reduce the number of administrations of propylthiouracil required to treat hyperthyroidism, the bioavailability and sustained-release characteristics of 300 mg propylthiouracil formulated in hydrophilic matrix tablets were evaluated after single oral administration in healthy male volunteers. A conventional tablet was chosen as the reference formulation.

For tablets formulated from three different types of hydroxypropylmethylcellulose, K15M, K4M and K100LV, propylthiouracil dissolution in-vitro was 40%, 51% and 100%, respectively, in 8 h. The three matrix formulations showed sustained plasma concentration-time profiles. The relative bioavailability was 50, 51 and 87%, respectively, for K4M, K15M and K100LV hydroxypropylmethylcellulose matrix tablets. When reverse triiodothyronine concentrations were plotted against the corresponding propylthiouracil concentrations, an antihysteresis loop was observed with the conventional tablets and the K100LV matrix tablet. A linear concentration-response curve was obtained for both the K4M and K15M formulations.

The results showed that the K100LV matrix tablet gave a sustained plasma concentration–time profile and a bioavailability and extrathyroidal effect similar to that of a conventional tablet.

Propylthiouracil, used to treat hyperthyroidism, is usually administered as 50-mg conventional tablets. Although there is some correlation between the plasma concentrations obtained 1 h after single administration of propylthiouracil (as measured by the area under the plasma concentration–time curve) and the chronic antithyroid effect (Kampmann & Molholm-Hansen 1981a), the relationship between the plasma concentration of propylthiouracil and its effect remains unclear. Propylthiouracil is concentrated in the thyroid gland (Lazarus et al 1975) and its duration of action is longer than measurable concentrations of propylthiouracil can be detected in plasma. Propylthiouracil has a half life of 40 to 120 min (Kampmann & Molholm-Hansen 1981b) and is usually administered 3 times a day in doses of 100 mg. Some authors have suggested that hyperthyroid patients can be treated satisfactorily with a single daily dose of 300 mg (Greer et al 1965) but Gwinup (1978) reported that a single daily dose was less satisfactory than dividing the dose over 3 administrations. This observation might be related to saturation of the uptake mechanism of propylthiouracil in the thyroid gland at higher plasma concentrations (Aungst et al 1979). To be able to reduce the number of administrations, it might thus be interesting to develop a sustained-release preparation, providing lower but more sustained plasma concentrations. In a previous paper we reported the influence of type of hydroxypropylmethylcellulose, source, polymer particle characterization, addition of fillers and tablet manufacturing parameters on the in-vitro release of propylthiouracil and the bioavailability of propylthiouracil from the matrix tablets in dogs and pigs (Kabanda et al 1994a).

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The purpose of this study was to evaluate the relative bioavailability in man of three matrix sustained-release formulations highly dosed with propylthiouracil. The bioavailability was compared with that of conventional tablets and the pharmacological effect was studied by measuring the plasma concentration of reverse triiodothyronine.

Materials and Methods

Formulations

Sustained-release tablets containing 300 mg propylthiouracil (Nycomed Christiaens, Brussels, Belgium) were formulated using three different grades of hydroxypropylmethylcellulose, Methocel K15M, K4M and K100LV (Colorcon, Orpington, UK). The hardness of the tablets was 118 ± 10 N (Heberlein, Wattwil, Switzerland); their diameter was 12 mm. The in-vitro dissolution profile was determined with the USP XXII Paddle Method II (US Pharmacopeial Convention 1990) at a rotational speed of 120 rev min^{-1} and in simulated intestinal fluid (pH 7·5).

Bioavailability of propylthiouracil in man

The trial was conducted in accordance with the Declaration of Helsinki and its subsequent modifications and the study was approved by the Medical Ethics Committee of the Medical School in Gent. To avoid repetitive administration of propylthiouracil in healthy subjects in view of the risk of agranulocytosis, each formulation was tested on a different set of volunteers. Eight healthy euthyroid male volunteers, 18–30 years old, were selected for each preparation; for the K100LV

formulation results were obtained from 7 volunteers only as one withdrew before drug administration. The volunteers gave written informed consent and were judged healthy on the basis of their past medical history, a physical examination, electrocardiogram and routine laboratory screening within 2 weeks before drug administration. Their thyroid status was assessed by determining the serum concentration of thyroid-stimulating hormone (TSH) and antithyroglobulin and anti-thyreoperoxidase antibodies. All subjects were non-smokers and medication-free; none had ever previously taken propylthiouracil.

Before administration of the drug an intravenous cannula was placed in one of the anticubital veins and a blank blood sample (6 mL) was obtained. The cannula was kept open by use of heparinized saline solution. Propylthiouracil (300 mg) was then administered orally with water (200 mL) between 0745 and 0845 h in the form of 6 conventional tablets (propylthiouracile 50 mg, Exel Pharma S.A./N.V., Brussels, Belgium) or one of the sustained-release matrix tablets containing 300 mg propylthiouracil and 30% K4M, 30% K15M or 30% K100LV. Blood samples (6 mL at each sampling) were withdrawn 0·5, 1, 1·5, 2, 3, 4, 6, 8, 10, 12, 14 and 24 h after intake into glass tubes containing 60 μL of heparin solution; the last 2 samples were not taken after administration of the conventional tablets. The subjects fasted from 12 h before the experiment but intake of water was allowed until 1 h before tablet administration. A standard breakfast, lunch and supper were provided 2, 5 and 10 h, respectively, after drug intake. From 2 h after drug intake, water was taken freely. The intake of alcoholic beverages was not allowed from 12 h before propylthiouracil administration until 24 h afterwards. Blood samples (6 mL) were collected in dry heparinized glass tubes and were centrifuged for 10 min at 2500 rev min^{-1} within 1 h after collection. Separated plasma was divided into two portions (2·5 mL and 0·5 mL); these were stored at − 20°C until assay for propylthiouracil (2·5 mL sample) or reverse triiodothyronine (0·5 mL sample). Plasma samples were analysed for propylthiouracil concentrations using a validated HPLC method (Kabanda et al 1994b).

The plasma concentrations of reverse triiodothyronine were determined by radioimmunoassay using a commercially available kit (Biodata, Milano, Italy).

Data analysis

Statistical analysis of the mean values was performed using non-parametric statistics. A P value < 0.05 was considered significant (Sokal & Rohlf 1991). C_{max} and t_{max} were determined from the individual plasma concentration–time curves by direct inspection. The area under the plasma concentration–time curve was calculated using the Absplots program (Shumaker et al 1988). AUC values were calculated from 0 to 12 h for the conventional tablets and from 0 to 24 h for matrix tablets. The relative bioavailability was calculated as (AUC_{0-24} sustained-release tablet/AUC_{0-12} conventional tablets) × 100. The reverse triiodothyronine concentrations were scheduled versus the corresponding propylthiouracil concentrations to investigate the concentration-dependency of the extrathyroidal effect of propylthiouracil (Bartle et al 1988).

Results

The in-vitro dissolution profile of conventional tablets and different hydrophilic matrix tablets containing 300 mg pro-

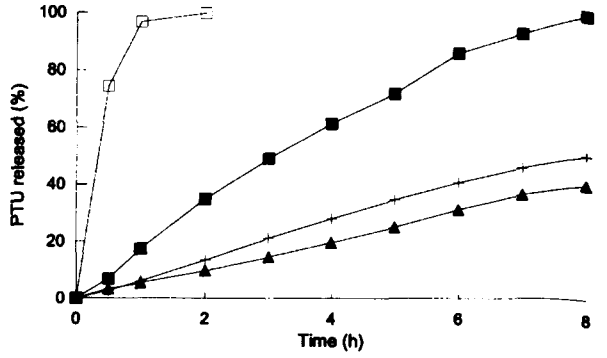

FIG. 1. In-vitro release profile of propylthiouracil from conventional tablets and from different hydrophilic matrix tablets containing 300 mg propylthiouracil (n = 3, s.d. < 6%). □ Conventional, ■ K100LV, + K4M, ▲ K15M.

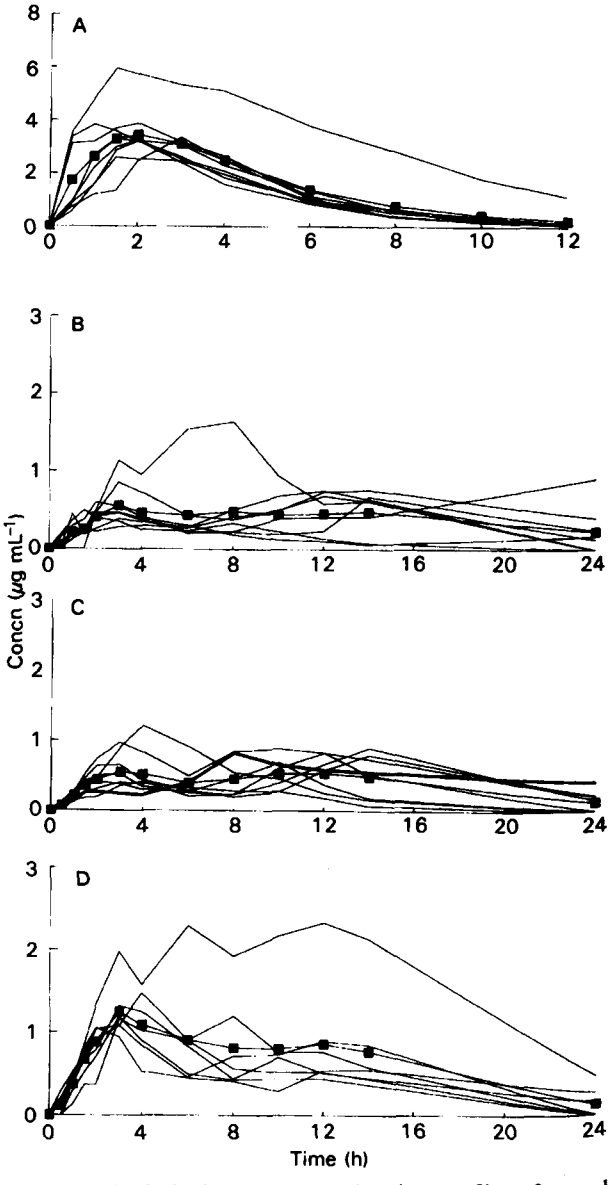

FIG. 2. Individual plasma concentration–time profiles after oral administration of propylthiouracil (300 mg) in man. A. Conventional, B. K15M, C. K4M, D. K100LV (n = 8 except for D, n = 7). For comparison, the mean curve (■) is also shown.

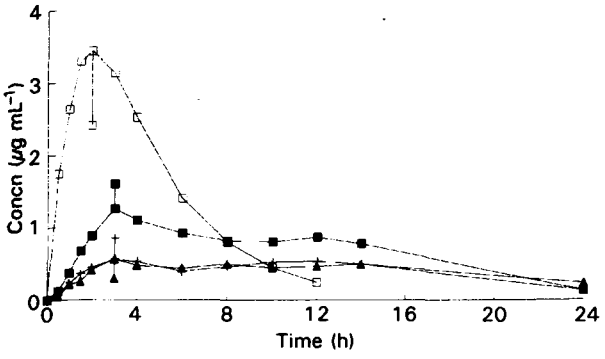

FIG. 3. Mean plasma concentration-time profiles after oral administration of propylthiouracil (300 mg) in man. □ Conventional, +K100LV, ■ K4M, ▲ K15M (n = 8 except for K100LV, n = 7). For clarity, the s.d. is only shown for the peak concentration.

pylthiouracil is shown in Fig. 1. For Methocel K100LV, the dissolution rate was 61% after 4 h and 100% after 8 h. For the K15M and K4M formulations slow in-vitro dissolution of propylthiouracil was observed, dissolution being 40% and 51%, respectively, after 8 h. The reference formulation was conventional tablets containing more than 95% propylthiouracil which dissolved within 1 h. Fig. 2 shows the plasma levels of propylthiouracil after administration of six conventional tablets (Fig. 2A), a K15M matrix tablet (Fig. 2B), a K4M matrix tablet (Fig. 2C) and a K100LV matrix tablet (Fig. 2D). The plasma concentration-time profiles showed a similar pattern for each formulation, except for one volunteer in the case of the conventional tablets, the K15M tablet and the K100LV tablet. The mean plasma concentrations for the different formulations are shown in Fig. 3, and C_{max}, t_{max} and AUC values are given in Table 1. The relative bioavailabilities of the K4M and K15M formulations were 50% and 51% respectively, whereas that of the K100LV formulation was 87%. The AUC value of the K100LV formulation was not significantly different from that of the conventional tablets. The reverse triiodothyronine levels increased as a function of plasma propylthiouracil concentration for all formulations (Fig. 4). An antihysteresis loop was obtained with the conventional tablets, whereas a steep concentration-response curve was obtained for the K4M and K15M formulations. An antihysteresis loop was also observed for the K100LV formulations.

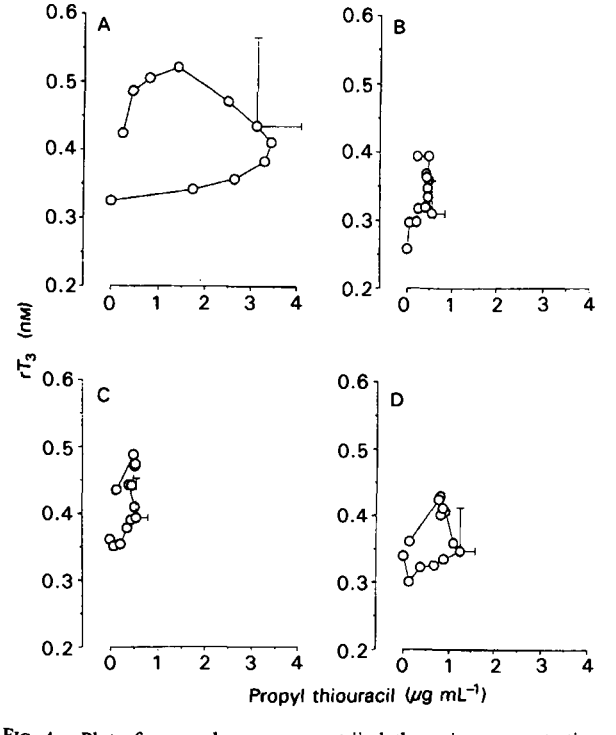

FIG. 4. Plot of mean plasma reverse triiodothyronine concentrations against plasma propylthiouracil concentrations. A. Conventional, B. K15M, C. K4M, D. K100LV. For clarity, the s.d. is only shown for the values obtained 3 h after propylthiouracil administration (n = 8 except for D, n = 7).

Discussion

A sustained-release formulation for propylthiouracil could offer advantages over a conventional formulation by improving patient compliance, reducing fluctuations on plasma concentration and providing better conditions for active uptake of propylthiouracil by the thyroid gland. The three hydroxy-propylmethylcellulose matrix tablets used were chosen because of their dissolution profile. All three led to clearly slower in-vitro propylthiouracil dissolution than the conventional tablets but there was clear distinction between the dissolution rate of the K100LV formulation on the one hand (100% after 8 h) and the K4M and K15M formulations on the other (approximately 50% after 8 h). Notwithstanding the similar in-vitro dissolution profile, the K4M and K15M formulations were both studied to compare their in-vivo behaviour. Both polymers have hydroxypropoxy and methoxy substitution (8·2% and 21·7%, respectively, for K4M and 8·9% and 22·8%, respectively, for K15M) but their very different nominal viscosity (5100 mPa s for K4M and 17 354 mPa s for K15M) might result in different erosional behaviour during their transit in the gastrointestinal tract. The in-vivo results showed important intersubject variability for all formulations, as has also been reported by other authors (Sitar & Hunnighake 1975; Cooper et al 1981). The plasma concentrations obtained with conventional tablets were comparable with those reported after single intake of 300 mg propylthiouracil in healthy volunteers (Cooper et al 1981). Although a sustained-release profile of plasma concentrations of propylthiouracil was obtained for the three matrix tablets, only for the K100LV formulation was the bioavailability comparable with that of the conventional tablets. In correlation with its faster dissolution rate in-vitro, a possible explanation for this phenomenon is the higher swelling rate and the higher erosion rate of the swollen gel-like layer of the K100LV matrix in comparison with the K4M and K15M tablets. The difference between the nominal viscosities of K4M and K15M seemed to have no influence on the in-vivo behaviour of the tablets. First-pass metabolism of propylthiouracil has been suggested (Kampmann & Skovsted 1974); the slower the rate of dissolution of the tablets and thus of passage of propylthiouracil to the liver, the more important this mechanism might be. Propylthiouracil has both intrathyroidal (inhibition of organification and coupling) and extrathyroidal (inhibition of the conversion of T_4 to T_3 and of reverse triiodothyronine to T_2) sites of action. Some correlation has been shown between propylthiouracil plasma concentrations and both antithyroid actions (Kampmann & Molholm-Hansen 1981a). The intrathyroidal action of propylthiouracil was not assessed in this study. Kampmann &

Molholm-Hansen (1981a) showed a correlation between the AUC, using C_{max} as an indicator, and the intrathyroidal effect of propylthiouracil. As the AUC of the K100LV tablet was similar to that of the conventional tablets, comparable intrathyroidal effects might be expected. The extrathyroidal effect of propylthiouracil was assessed by measuring the elevation of reverse triiodothyronine in plasma (Laurberg & Weeke 1978). When Bartle et al (1988) plotted reverse triiodothyronine concentrations as a function of propylthiouracil concentrations they found a linear concentration–effect relationship when the propylthiouracil plasma concentrations rose slowly; the AUC was low after rectal administration of propylthiouracil. In contrast, a counter-clockwise hysteresis was observed with orally administered conventional tablets; this was also confirmed in our study, illustrating that the propylthiouracil concentrations, when rising quickly, are not in equilibrium with the reverse triiodothyronine response. The administration of the K100LV tablet also led to a hysteresis curve for the relationship between propylthiouracil concentration and reverse triiodothyronine response, confirming that the plasma concentration profile of propylthiouracil for this matrix more closely resembled that of the conventional tablets than those of the K4M and K15M tablets.

In conclusion, the administration of a sustained-release formulation of propylthiouracil with hydroxypropylmethylcellulose Methocel K100LV yielded a sustained plasma concentration profile; the bioavailability and the propylthiouracil concentration–reverse triiodothyronine response relationship were comparable with those of the conventional tablets. The K100LV tablet might be suitable for use in antithyroid therapy

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