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ORIGINAL ARTICLE

Liver Volume, Portal Vein Flow, and Clearance of Indocyanine Green and Antipyrine in Hyperthyroidism before and after Antithyroid Treatment

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Background: The aim of the study was to examine liver volume, portal vein flow, and indocyanine green (ICG) and antipyrine clearance in hyperthyroidism before and after antithyroid drug treatment. **Methods:** Liver volume and blood flow in the portal vein were investigated in nine fasting patients with hyperthyroidism by means of computed tomography scan and Doppler ultrasound, respectively. ICG clearance was estimated by bolus injection of ICG (0.5 mg/kg body weight) and antipyrine clearance with a one-sample technique. All patients were investigated before and after 3 months of antithyroid treatment, when euthyroidism had been achieved. The Wilcoxon matched-pairs test was used for statistical analysis. **Results:** The median liver volume increased by 238 (155–289) ml (median, 95% confidence interval), corresponding to 19%, and the weight by 5.0 (0.0–8.0) kg (8%), and the antipyrine clearance decreased by 8 (3.1–34.4) ml/min (16%). These changes were all significant ($P < 0.05$). The relation between liver volume and body weight increased from 19.9 (16.5–23.7) ml/kg to 21.4 (17.1–21.9) ml/kg ($P = 0.11$). The liver blood flow as estimated by ICG clearance and Doppler ultrasound was not altered significantly after the treatment period ($P = 0.07$ and 0.77, respectively). **Conclusions:** The liver volume increased by 19% in nine hyperthyroid patients during treatment with antithyroids. Antipyrine clearance was reduced by 16%, whereas liver blood flow, as estimated by ICG clearance and Doppler ultrasound examination of portal-vein flow, was not significantly altered. A differential regulation of liver volume and oxidative metabolic capacity in hyperthyroidism was seen.

Key words: Antipyrine clearance; computed tomography scan; Doppler ultrasound; drug metabolism; hyperthyroidism; indocyanine green; liver blood flow; liver volume; pharmacokinetics; portal vein flow

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Thyroid disorders have an effect on hepatic function. Abnormalities in liver function tests are occasionally found in thyroid disorders (1–4), and even hepatomegaly has been reported in up to 33% of patients with hyperthyroidism without any obvious reason (1–3). Thyroid disorders are further known to influence the pharmacokinetics of several drugs (5, 6).

Although hepatomegaly can be found clinically in thyrotoxicosis, no studies addressing this question exist. Moreover, the knowledge about hepatic blood flow is scarce. When the high-clearance drug propranolol was used, increased clearance was seen (7), whereas hepatic blood flow was found to be normal in hyperthyroid patients compared with healthy subjects when using the Fick principle by means of the bromsulphophthalein test (8). However, the induction of hepatic oxidative drug metabolism in hyperthyroidism is well known. Thus, the clearance of the model drug antipyrine is increased and normalized during treatment (5, 9–13).

In cross-sectional investigations a positive correlation was found between antipyrine clearance and liver volume in healthy adults (14). However, during rifampicin, phenobarbital, or glutethimide induction in man, antipyrine clearance increased markedly, with no or only minor changes in either liver volume or blood flow (15–17).

Thus, the present study was done to characterize the influence of thyrotoxicosis on liver volume, oxidative metabolic capacity, and hepatic blood flow.

Subjects and Methods

Subjects

Hyperthyroidism was diagnosed by clinical manifestations

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Table I. Clinical and biochemical characteristics of nine hyperthyroid patients before and after antithyroid treatment. Subjects were recruited among the patients in the medical departments at two hospitals with different analytical methods for thyroid hormones, thus the differing reference values.

				Hyperthyroid				Euthyroid			
Subject	Sex	Aetiology	Age, years	TSH*, mU/l	T_3 (total), nmol/l	Resin-T_3	T_4, nmol/l	TSH *, mU/l	T_3 (total), nmol/l	Resin-T_3	T_4, nmol/l
E.H.	M	Struma diffusa toxica	37	<0.005	8.6	2.00	241†	0.012	2.4	1.10	89†
L.K.	F	Struma diffusa toxica	50	<0.005	5.8	1.67	164†	0.005	1.6	1.14	52†
C.S.¶	M	Struma diffusa toxica	50	0.006	7.8	1.50	267†	–	–	–	–
C.C	F	Struma diffusa toxica	23	0.013	10.2	1.56	209†	0.006	3.1	0.83	50†
S.C.	F	Struma diffusa toxica	32	<0.005	9.0	1.43	237†	3.4	2.0	0.73	50†
Normal range§				0.30–3.7	1.0–2.5	0.80–1.25	56–129†	0.30–3.7	1.0–2.5	0.80–1.25	56–129†
L.A.	F	Struma nodosa toxica	67	<0.02	3.9	–	33.8‡	3.52	1.8	–	5.5‡
E.R.	F	Struma nodosa toxica	83	<0.02	2.6	–	55.4‡	<0.02	1.8	–	20.0‡
B.L.	F	Struma diffusa toxica	51	<0.02	2.7	–	36.0‡	0.392	1.5	–	12.9‡
A.P.	M	Struma diffusa toxica	33	<0.02	5.4	–	47.0‡	<0.02	1.9	–	11.5‡
C.S.¶	M	Struma diffusa toxica	50	–	–	–	–	<0.02	2.4	–	8.5‡
Normal range‖				0.17–2.87	1.1–2.5		7.7–28‡	0.17–2.87	1.1–2.5		7.7–28‡

TSH = thyroid-stimulating hormone.
† Total T_4
‡ Free T_4
§ Normal range for the first patients.
‖ Normal range for the last patients.
¶ This subject had laboratory tests taken at both hospitals.

and laboratory tests. Exclusion criteria were pregnancy, age less than 18 years, any known liver disorder or significant medical disease, prior abdominal irradiation, regular drug treatment, suspected pituitary gland disease, or autoimmune thyroiditis.

Nine outpatients entered the study, three men and six women (Table I). The patients were recruited from two different hospitals. One patient (C.S.) had blood samples taken at both hospitals. Three were smokers, and none had a daily alcohol consumption. All the investigations were performed within 10 days of the diagnosis and preferably before initiation of the medical treatment and were repeated 14 weeks later, when the patients were euthyroid both clinically and biochemically (normalized T_3 and T_4). The patients had fasted for at least 4 h before the investigations. Three were treated with propylthiouracil, and the others with thiamazole. None received beta-blocking agents. Weight and height were recorded.

Ethical considerations

All patients gave written informed consent. The project was approved by the local ethics committee (KA 95118). The study was performed in accordance with the Declaration of Helsinki.

Ultrasound

The portal vein flow was determined by using a Duplex system (ultrasound scanner type 3535, B&K Medical A/S, Gentofte, Denmark). The subjects were examined with a 3.5-MHz curved-array transducer in the supine or left lateral position from the epigastric (lower part of the vein) or intercostal (upper part of the vein) approach. The portal vein was localized and its internal diameter measured on a longitudinal B-mode scan, to calculate the cross-sectional area. The insonation angle of the pulsed Doppler line was kept as small as possible, if possible less than 60 °, and the Doppler sample volume was adjusted to contain the total vein lumen. Using a low filter (100 Hz), an average of the flow velocity was measured and multiplied by the cross-sectional area of the vein to obtain the flow rate in millilitres per minute. The mean value of five measurements was used, apart from one examination in which only one measurement was possible. The two examinations for each patient were made with exactly the same technique, keeping the same ultrasound approach and the same insonation angle. One observer made all measurements.

Computed tomography scan

The computed tomography (CT) examinations were

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Table II. Liver volume investigated by means of computed tomography scan, antipyrine clearance with a one-sample technique, body weight, indocyanine green clearance by means of bolus injection, and portal vein flow with Doppler ultrasound of nine patients with hyperthyroidism. All patients were investigated before and after 3 months of antithyroid treatment, when euthyroidism was achieved. Median and 95% confidence interval (CI) for the median, using ranks of the observations, are shown. The Wilcoxon matched-pairs test was used to test variables for differences before and after treatment.

	n	Hyperthyroid, median (CI)	Euthyroid, median (CI)	Difference, median (CI)	*P* value
Liver volume, ml	9	1239 (1022–1509)	1415 (1312–1747)	238 (155–289)	<0.05
Body weight, kg	9	65.0 (58–72)	66.0 (60–90)	5.0 (0.0–8.0)	<0.05
Liver vol/body weight, ml/kg	9	19.9 (16.5–23.7)	21.4 (17.1–21.9)	1.1 (−1.7 to 4.2)	0.11
Antipyrine clearance, ml/min	7	49.0 (32.1–76.6)	37.9 (28.1–58.7)	−8.2 (−3.1 to −34.4)	<0.05
ICG clearance, ml/min	9	991 (688–1248)	742 (577–1262)	−56 (−484 to 271)	0.77
Portal vein flow, ml/min	8	950 (500–1736)	709 (473–1063)	−184 (−733 to 112)	0.07

performed with a Picker PQ-2000 machine (Picker International, Cleveland, Ohio, USA) as serial axial slices, 10 mm thick, 10 mm from the diaphragm throughout the liver. The patients received no contrast medium. The area of each slice of liver tissue was measured by planimetry. The volume of each slice was calculated by multiplication of the slice height; the liver volume was then calculated as the sum of the volume of each slice. Two observers measured all scans, and the mean value was used.

Pharmacologic investigations

Indocyanine green clearance. Indocyanine green (ICG) at a dose of 0.5 mg/kg body weight was given as an intravenous bolus injection (18–20). Blood was collected from the contralateral arm at 3-min intervals until 15 min and then at 20 min after injection. ICG plasma levels were measured by high-performance liquid chromatography (HPLC) (21), and clearance calculated from the dose divided by the area under the curve (AUC), using a computerized program.

Antipyrine clearance. Antipyrine clearance was estimated with a one-sample method (22). Antipyrine, 1000 mg, was administered orally, and blood was sampled from 13 to 29 h later. Antipyrine was analysed by HPLC, and clearance was calculated using the estimated volume of distribution (22).

Statistical methods

The Wilcoxon matched-pairs test was used. The confidence interval (CI) for the median (95%) was obtained using ranks of observations (23).

For the CT scan measurements the mean of the differences of the two observers, 95% CI, and the standard deviation of the difference were calculated. For the Doppler ultrasound measurements the standard deviation (*s*) of the five measurements for each subject was calculated. The intrapersonal variation of the five flow measurements was calculated by using a one-way analysis of variance (ANOVA).

Statistical analysis was done by the computer program manual Statistics for Windows (1996) (StatSoft, Inc., Tulsa, Okla., USA).

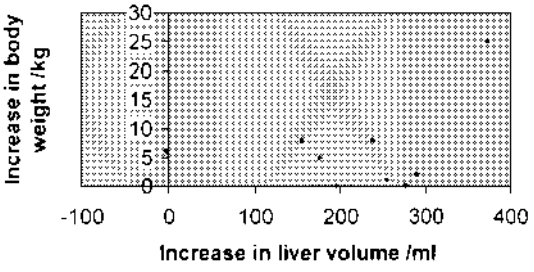

Fig. 1. Increase in body weight and liver volume for nine patients with hyperthyroidism during treatment. All patients were investigated before and after 3 months of antithyroid treatment, when euthyroidism was achieved.

Results

Table II shows the variables at the time of diagnosis and after 3 months of treatment. The median liver volume increased by 238 (155–289) ml (median, 95% CI), and the weight by 5.0 (0.0–8.0) kg, corresponding to 19% and 8%, respectively. The antipyrine clearance decreased by 8 (3.1 to 34.4) ml/min, corresponding to a decrease of 16%. These changes were all significant ($P < 0.05$).

An increase was also found in the coefficient liver volume/body weight, from 19.9 (16.5–23.7) ml/kg to 21.4 (17.1–

Table III. Liver volume investigated by means of computed tomography scan, body weight, and the alteration in these variables during treatment in nine patients with hyperthyroidism. All patients were investigated before and after 3 months of antithyroid treatment, when euthyroidism was achieved

Patient	Liver volume, ml	Body weight, kg	Increase in liver volume, ml	Increase in body weight, kg
E.H.	1390	69.8	−3	6.2
C.S.	1569	95.0	155	8.0
A.P.	1509	72.0	238	8.0
L.K.	1239	60.0	176	5.0
L.A.	1231	52.0	276	0.0
E.R.	936	66.0	195	0.0
B.L.	1548	65.0	373	25.0
S.C.	1023	58.0	289	2.0
C.C.	1072	61.0	254	1.0

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21.9) ml/kg, although statistical significance was not reached ($P = 0.11$). Fig. 1 and Table III show the alteration in body weight and liver volume in the individual patients. Apart from two, all patients showed an increase in liver volume of 150–300 ml, the increase being independent of the weight gain.

The liver blood flow, as estimated by means of ICG clearance and Doppler ultrasound was not altered significantly after the treatment period (Table II).

Interobserver variation. For the CT scan measurements the mean of the differences of the two observers was 14 ml (1.7–26.3, 95% CI) (32, standard deviation of the difference).

Intrapersonal variation. For the Doppler ultrasound measurements, the *s* of the five measurements of each subject varied between 16 ml/min and 253 ml/min. The ANOVA showed that the within-group mean square (the intrapersonal variation) was 4.02 $(ml/s)^2$; thus the residual standard deviation was 120 ml/min.

The Doppler ultrasound examination had to be omitted in one patient because of excessive abdominal fat, and the antipyrine clearance was not performed in two patients owing to lack of co-operation.

Discussion

The present study showed a considerable increase in liver volume after antithyroid treatment. This finding has to our knowledge never been reported previously. In healthy subjects liver volume has been shown to correlate with body weight (24), and the weight gain seen in our patients was expected to explain the increase in liver size. However, this was not the case in these patients with treated thyrotoxicosis, since the increase in liver volume was relatively constant and independent of the weight gain, as can be seen in Fig. 1. This finding was supported by the increase in the coefficient liver volume/body weight. Although not significant, it indicates that the increase in liver volume could not be explained only by the weight gain.

It is well known that the antipyrine clearance is increased in hyperthyroidism and normalized during treatment (5, 9–13). Our antipyrine data corroborate these results.

No significant changes in liver blood flow were found after antithyroid treatment, as estimated by ICG clearance and Doppler ultrasound. Existing data are, as mentioned earlier, conflicting. The results of this study support the earlier findings obtained with the bromsulphophthalein test and hepatic vein catheterization (8) but are in contrast to the increased clearance of propranolol found in thyrotoxicosis (7). ICG is routinely used as a model substrate for the estimation of hepatic plasma flow (18, 20), although the quantitative assessment is difficult (25–27). Doppler ultrasound is encumbered with some unreliability owing to lack of laminar flow in the portal vein, uncertainty in the size of the average vein area, and the observer variability (28–31). Consequently, as indicated by the CI, minor alterations in the blood flow will not be detected by these methods.

Our results show a concomitant decrease in antipyrine clearance and increase in liver size in the individuals during treatment of thyrotoxicosis. This is in contrast to the positive correlation between liver size and antipyrine clearance in healthy volunteers shown by several authors (14, 32, 33). However, after induction with rifampicin and phenobarbital a selective increase in antipyrine clearance is seen, with no or only minor change in liver volume (16, 17). Thus, our results indicate a differential regulation of liver volume and oxidative metabolic capacity also in hyperthyroidism.

The age of the patients varied between 23 and 83 years. Due to the study design, the effect of antithyroid treatment on the antipyrine clearance and liver volume is shown, although both decrease with advanced age (32–36).

In conclusion, the present study has shown a considerable increase in liver volume in hyperthyroid patients during antithyroid treatment. Further studies are needed to elucidate the nature of this alteration in liver volume. A decrease in antipyrine clearance in the euthyroid state was confirmed, as expected. It was also found that the clearance of antipyrine did not correlate with liver size in individual patients after antithyroid treatment, suggesting a differential regulation of liver size and drug metabolizing capacity in thyrotoxicosis. Eventually, no significant alteration in hepatic blood flow during thyrotoxicosis was found.

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