The Effect of Iopanoic Acid on Thyrotropin Secretion in Patients with Cirrhosis of the Liver

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Abstract

Ten patients with liver cirrhosis and six normal subjects were studied to evaluate the effect of iopanoic acid (IA) on thyrotropin secretion. A thyrotropin-releasing-hormone (TRH) test was performed before and 5 days after IA administration (single oral dose of 3 g). After IA administration, a significant increase in TSH response to TRH was observed in normal subjects. In cirrhotics, however, it did not significantly increase after IA administration. The serum T3 and T3/TBG ratio were significantly decreased and the serum T4 and T4/TBG ratio were increased after IA administration in normal subjects and cirrhotics. There was no significant difference in the % decrease in serum T3, % increase in serum T4 or other thyroid hormone parameters including TSH in IA induced TSH responders (R) and non-responders (NR). However, r-T3 before and after IA in R was higher than those in NR. The values for hepatic function tests such as serum albumin, prothrombin time, 45 minutes retention rate of bromsulphalein (BSP45 min) and the cholinesterase (ChE) level in R were not different from those of NR.

These results suggested that in cirrhotics, abnormal regulation of the hypothalamo-pituitary system might exist.

It has been frequently reported that patients with liver cirrhosis have functional abnormalities in the hypothalamo-pituitary system (Green et al., 1977; Mowat et al., 1976). If cirrhotics have such abnormal regulation, the pituitary might be unable to secrete TSH in response to the changes in the circulating triiodothyronine (T3) concentration. In such circumstances, it might be difficult to make a diagnosis of primary hypothyroidism. However, in patients with liver cirrhosis, the regulation of TSH secretion has not been fully examined yet.

On the other hand, recent experiments have shown that iopanoic acid (IA), an oral cholecystographic agent, inhibits the conversion of thyroxine (T4) to T3 in the pituitary of the rat (Larsen et al., 1979) and peripheral tissue (Burgi et al., 1976), and increases the response of thyrotropin (TSH) to thyrotropin-releasing-hormone (TRH) in normal subjects (Kleinman et al., 1980). The increase in TSH response to TRH induced by IA is attributed to the decrease in circulating T3 or inhibitory effects of
IA on pituitary conversion of T4 to T3 (Kleinmann et al., 1980).

The purpose of this study was to evaluate the regulation of TSH secretion in patients with liver cirrhosis, using a TRH test performed before and after IA administration.

Patients and Methods

After informed consent was obtained, ten patients with liver cirrhosis (6 males and 4 females, aged 32-60) and six normal subjects (3 males and 3 females, aged 35-60) were studied. The diagnosis of liver cirrhosis was based on liver scintigram, peritoneoscopy, histological features and various laboratory tests including the 45 minute retention rate of bromsulphalein (BSP_{45\text{ min}}), total bilirubin, glutamyl oxaloacetic transaminase (GOT), glutamyl pyruvic transaminase (GPT), albumin, gamma-globulin, cholinesterase (ChE) and prothrombin time. They were all in a compensated state without ascites or encephalopathy. The cause of cirrhosis was viral infection in all cases (hepatitis B, 7 cases and hepatitis non-A non-B, 3 cases) (Table 1).

A TRH test was performed before and 5 days after a single 3g oral dose of IA (Telepaque®, Nihon Shoji Co., Osaka, Japan). There was an interval of at least 1 week between the first and second TRH tests.

At the time of the study, all subjects were judged to be in a steady state having no evidence of renal failure, starvation or depression. No medication such as steroid or dopamine, which suppressed TSH response to TRH, was administered. After an overnight fast, venous blood for thyroid hormones and TSH was obtained at 0:00h. The TRH test was performed as follows: an intravenous heparinized cannula was inserted into a forearm vein of the subjects at rest 30 minutes before the test. At time 0, venous blood was obtained for determination of T3, T4, reverse T3 (r-T3) and TSH, and this was immediately followed by a bolus injection of 250 μg of synthetic TRH (Tanabe Pharm. Co, Ltd., Tokyo). Blood samples were taken 20 min, and 60 min after TRH injection for determination of TSH. Serum was separated and stored at -20°C until the assay. Blood samples were analysed with commercially available radioimmunoassay kits for T3, T4, TSH (Amersham International plc., England), r-T3 (Dainabot Radioisotope Laboratory, Tokyo) and thyroxine-binding globulin (TBG) (Hoechst Japan Inc., Tokyo). Measurements were carried out in duplicate and all samples were assayed concurrently. Normal ranges in this laboratory are 4.5-12.0 μg/dl for T4, 0.7-2.1 ng/ml for T3, 240-320 pg/ml for r-T3, 1.1-5.0 μU/ml for TSH and 12.9-22.5 μg/ml for TBG. The limit of detectability of TSH was 1.1 μU/ml. For the five hormone measurements, the intraassay coefficients of variation were 5.5% for T4, 6.0% for T3, 5.8% for r-T3, 8.0% for TSH and 9.0% for TBG. The interassay coefficients of variation were 7.5% for T4, 7.0% for T3, 8.0% for r-T3, 8.0% for TSH and 9.0% for TBG. The T3/TBG ratio and T4/TBG ratio were calculated according to the following equations: T3/TBG ratio = T3 (ng/
ml)/TBG (μg/ml)×100, T4/TBG ratio=T4 (μg/dl)/
TBG (μg/ml)×10. The area under the TSH’s
concentration-time curve (integrated TSH re-
sponse) was measured by the trapezoidal rule.
Results were expressed as mean±standard error
(SE). Statistical significance was determined by
the Mann-Whitney U test between groups and
Wilcoxon matched-pairs signed-ranks test within
each group.

Results

The TSH response to TRH in normal
subjects before and after the administration
of IA is shown in Figure 1 (left panel). Normal subjects had a significant increase
in TSH response to TRH after IA adminis-
tration. In cirrhotics, however, TSH re-
sponse did not significantly increase after
IA administration (Fig. 1, right panel). The
large SE of cirrhotics was explained by the
fact that 3 patients (case 3, 4, 6) had an
exaggerated TSH response of TSH to TRH.
The increase in integrated TSH response
(ΔTSH) after IA in normal subjects was
332.0±49.6, while that in cirrhotics was
138.4±48.7 (normal subjects vs cirrhotics,
p<0.05). Three patients (cases 8–10) had

Fig. 1. TRH stimulated TSH response before and after IA administration. Left panel: normal
subjects, right panel: cirrhotics, NS: not significant Values were expressed as mean±SE
(standard error).
a significant increase in TSH response after IA administration similar to normal subjects ($\Delta$TSH $348.7 \pm 68.9$). However, the $\Delta$TSH of the remaining 7 cases was $48.7 \pm 15.6$. Table 2 shows the IA induced % decrease in serum T3 and % increase in serum T4. There was no significant difference between the % decrease in serum T3 or % increase in serum T4 in normal subjects and cirrhotics. However, the serum T3 level, T3/TBG ratio, T4 level and T4/TBG ratio in liver cirrhosis were lower than those of normal subjects. The changes in T3 and T4 after IA administration reflected those of the T3/TBG ratio and T4/TBG ratio in both normal subjects and cirrhotics. The TBG concentration before IA administration (13.9 $\pm$ 4.5 $\mu$g/ml) was not different from that after IA (14.6 $\pm$ 5.2 $\mu$g/ml) in cirrhotics. The integrated TSH response ($\Sigma$TSH) before IA administration was similar in both normal subjects and cirrhotics, but $\Sigma$TSH after IA administration in cirrhotics increased less than that of normal subjects.

This difference between TSH response to TRH in normal subjects and cirrhotics arose from the fact that in 7 of 10 cirrhotics, TSH response to TRH did not sufficiently increase after IA administration compared with normal subjects. The maximum serum TSH increase after IA administration in normal subjects was 11.0 $\pm$ 3.7 $\mu$U/ml (mean $\pm$ SD). Accordingly, the lack of augmentation was defined to be less than 3.6 $\mu$U/ml ($-2SD$) of the maximum TSH increase.

The patients were divided into two groups; IA-induced TSH responders, in which the maximum serum TSH increase after IA was more than 3.6 $\mu$U/ml (case 8—10, R), and non-responders, in which that was less than 3.6 $\mu$U/ml (case 1—7, NR). The serum T3, T3/TBG ratio, T4, T4/TBG ratio, r-T3 and TSH for the two groups were compared. As shown in Table 3, IA-induced % decrease in serum T3, % increase in serum T4, T3/TBG ratio, T4,
### Table 3. Basal thyroid hormone levels in patients of non-responder (NR) and responder (R)

| Case | Age | Sex | T3 (ng/ml) | T4 (µg/dl) | r-T3 (pg/ml) | TSH (µU/ml) | ∑TSH | T3 % decrease | T3 % increase | T4 % decrease | T4 % increase | T3/TBG ratio | T4/TBG ratio |
|------|-----|-----|------------|------------|--------------|-------------|-------|----------------|--------------|---------------|---------------|--------------|--------------|--------------|
|      |     |     | B | A | B | A | B | A | B | A | B | A | B | A |
| 1    | 52  | M   | 1.10 | 0.70 | 7.5 | 9.3 | 255.3 | 487.8 | 2.7 | 2.3 | 428 | 456 | 36 | 24 | 5.7 | 3.6 | 3.9 | 4.8 |
| 2    | 59  | F   | 0.60 | 0.40 | 4.6 | 5.5 | 239.0 | 550.5 | 2.9 | 0.8 | 434 | 362 | 33 | 20 | 5.8 | 3.8 | 4.4 | 5.2 |
| Nonresponder (NR) |     |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 3    | 41  | M   | 1.65 | 0.85 | 7.1 | 9.4 | 234.3 | 326.3 | 6.7 | 7.4 | 1622 | 1654 | 48 | 32 | 6.7 | 3.7 | 2.9 | 4.1 |
| 4    | 60  | F   | 1.22 | 0.64 | 8.0 | 10.8 | 219.0 | 598.5 | 4.4 | 3.1 | 1192 | 1252 | 48 | 35 | 6.7 | 2.9 | 4.4 | 4.8 |
| 5    | 60  | F   | 0.40 | 0.40 | 2.7 | 3.4 | 231.4 | 305.5 | 2.6 | 3.1 | 442 | 474 | 0  | 26 | 4.7 | 4.7 | 3.1 | 4.0 |
| 6    | 53  | M   | 0.85 | 0.60 | 4.5 | 5.9 | 240.0 | 450.5 | 7.4 | 9.0 | 1451 | 1589 | 30 | 31 | 7.7 | 5.3 | 4.1 | 5.2 |
| 7    | 55  | M   | 0.71 | 0.44 | 5.0 | 7.0 | 251.0 | 500.1 | 6.5 | 7.5 | 742 | 792 | 38 | 40 | 6.0 | 3.6 | 4.2 | 5.7 |
| Mean |     |     | 0.93 | 0.58 | 5.6 | 7.4 | 238.5 | 459.9 | 4.7 | 4.7 | 902 | 940 | 33 | 30 | 6.2 | 3.9 | 3.9 | 4.8 |
|      |     |     | p<0.01 | p<0.02 | p<0.01 | NS | NS | p<0.01 | p<0.02 |     |     |     |     |     |     |     |     |     |
| Responder (R) | 8   | 40  | M   | 0.64 | 0.61 | 6.9 | 9.2 | 360.3 | 631.7 | 1.0 | 5.6 | 444 | 670 | 5  | 33 | 3.8 | 3.6 | 4.1 | 5.4 |
| (n=3) |     |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 9    | 32  | F   | 0.46 | 0.29 | 3.3 | 5.0 | 364.3 | 793.7 | 1.1 | 3.8 | 142 | 456 | 37 | 51 | 4.0 | 2.5 | 2.9 | 4.4 |
| 10   | 53  | M   | 0.43 | 0.26 | 3.8 | 4.5 | 373.9 | 769.0 | 4.0 | 4.4 | 450 | 956 | 40 | 18 | 4.9 | 2.7 | 4.4 | 4.7 |
| Mean |     |     | 0.51 | 0.39 | 4.7 | 6.2 | 366.1 | 731.4 | 2.0 | 4.6 | 345 | 694 | 27 | 34 | 5.1 | 3.6 | 3.8 | 4.8 |
|      |     |     | p<0.05 | p<0.02 | p<0.01 | p<0.05 | p<0.01 | p<0.05 | p<0.01 |     |     |     |     |     |     |     |     |     |
| NR vs R |     |     | NS | NS | NS | NS | p<0.05 | p<0.01 | NS | NS | NS | NS | NS | NS | NS | NS | NS |

- B: before administration of IA
- A: after administration of IA
- ∑TSH: integrated TSH response
- T3/TBG ratio, T4/TBG ratio: see text

T3 % decrease: IA induced % decrease in serum T3
T4 % decrease: IA induced % increase in serum T4
T4/TBG ratio, basal TSH and ΣTSH in R were not different from those of NR, but r-T3 before and after IA in R were higher than those in NR.

Values obtained in hepatic function tests in NR were compared with those of R. There was no significant difference, particularly in albumin (R 3.6±0.4, NR 4.0±0.4 g/dl), in ChE (136.7±15.5 vs 174.3±22.2 U/L), in prothrombin time (14.3±0.4 vs 13.6±0.9 seconds) or BSP 45 min (29.2±1.6 vs 23.5±2.4%). However, the results of hepatic function tests of NR tended to be better than those of R.

Three patients with an exaggerated response of TSH to TRH before IA were all non-responders, while 4 of 7 patients with a normal response to TRH before IA were non-responders.

Discussion

The present study demonstrated that IA had an inhibitory effect on the conversion of T4 to T3 and increased the TSH response to TRH in normal subjects. Our results agree with those of previous reports (Burgi et al., 1976; Kleinmann et al., 1980). These changes in thyroid hormones might be due to a decrease in iodothyronine-5'-deiodinase activity, resulting in a decrease in the generation of T3 from T4 (Kaplan and Utiger, 1978). A decrease in the cellular uptake of T4 in the presence of IA was also reported (Green and Bellamy, 1977).

The major finding of the present study was that in some cirrhotics, IA administration did not sufficiently increase the TSH response to TRH. This observation led us to speculate that the abnormal regulation of TSH secretion might exist in cirrhotics. In normal subjects, the increase in TSH response to TRH induced by IA might be attributed to an IA-induced decrease in circulating T3 or intrapituitary T3. A possible mechanism of such an abnormality is that the hypothalamic-pituitary system in cirrhotics may be unable to detect a decrease in serum T3 or intrapituitary T3. Another possibility is that the thyrotroph cell is not able to secrete TSH in spite of its ability to sense a decrease in circulating T3 or intrapituitary T3. The former explanation seems plausible because the TRH induced TSH response in cirrhotics was sufficient before IA administration though its pattern was delayed. This speculation may be supported by showing that other agents which lower the serum thyroid hormone level (PTU, iodine) and augment TSH release to TRH produce similar results in cirrhotics. Further investigation will be necessary.

Generally, the TSH response to TRH in cirrhotics is likely to be normal (Chopra et al., 1974; Hassabalch et al., 1981). However, Green et al. (1977) reported that the delayed TSH response to TRH, which was often seen in patients with hypothalamic or renal disease, was found in cirrhotics. They suggested that these abnormalities were attributed to the defective regulation of TSH secretion by the hypothalamus. In cirrhotics, abnormal hypothalamic regulation of gonadotropin secretion was also reported (Mowat et al., 1976). Therefore, the delayed TSH response to TRH before IA administration in cirrhotics observed in the present study was thought to be due to the abnormal hypothalamic regulation.

The TSH responders and non-responders could not be distinguished from the values for the serum T3, T4 levels, T3/TBG ratio, T4/TBG ratio, % decrease in serum T3, % increase in serum T4 or liver function tests. Other factors except circulating thyroid hormones and liver function tests might cause the abnormal regulation of TSH secretion in cirrhotics. The difference between the conversion rate of intrapituitary T4 to T3 in normal subjects and cirrhotics may be related to the lack of response to TRH. However, it was impossible to ascertain whether or not IA inhibited conversion of
T4 to T3 in the human pituitary gland.

It was reported that the increased r-T3 concentration might inhibit or at least prevent an increase in TSH secretion, since r-T3 inhibited the rat pituitary secretion in vitro (Chopra et al., 1978). However, r-T3 administration did not inhibit TSH secretion in humans (Nicod et al., 1976; Shulkin and Utiger, 1984). Our results demonstrated that there was no difference between the r-T3 concentration in normal subjects and that in cirrhotics after IA administration, and that the r-T3 of responders was higher than that of non-responders. From these results, it appears unlikely that r-T3 might inhibit or prevent TSH secretion.

A question raised in our study is why patients with liver cirrhosis are “euthyroid” in spite of decreased T3. The liver has been recognized as an important site in the peripheral metabolism of thyroid hormones (Oppenheimer et al., 1968), particularly in monodeiodination of T4 to T3 (Pittman et al., 1971). It has been shown that the patients with liver cirrhosis had a reduction in the peripheral conversion of T4 to T3 (Nomura et al. 1975), and showed a decrease in serum T3, the so-called “the low T3 syndrome”. Since T3 had the biological function of a thyroid hormone in man (Ingbar and Braverman, 1975), low T3 in cirrhotics could readily be interpreted as hypothyroidism. However, cirrhotics are considered to be euthyroid despite of a low T3 level (Chopra et al., 1974), and this idea is supported by clinical symptoms, normal basal TSH and normal TRH stimulated TSH response (Hassabalch et al., 1981). However, some investigators reported that patients with hepatic cirrhosis had a prolongation of the relaxation time of Achilles tendon reflex (Chopra, 1976), which was compatible with hypothyroidism. In our patients, no symptom suggesting hypothyroidism was seen.

In the light of results of the present study, the lack of an increase in the serum TSH concentration might not be taken as clear-cut evidence of euthyroidism in cirrhosis with primary hypothyroidism. However, the present study was only preliminary, so further examination should be necessary.

References


