Control of Thyroid Hormone Secretion in Normal Subjects Receiving Iodides

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ABSTRACT The administration of exogenous iodides (saturated solution of potassium iodide, SSKI) to normal male volunteers resulted in a significant decrease in the serum concentration of thyroxine (T_4) and triiodothyronine (T_3) and a significant increase in serum concentration of thyrotropin (TSH). During the control period (phase I), serum concentrations of T_4 averaged 6.9 ± 1.8 $\mu\text{g}/100$ ml (mean $\pm$ SD), T_3 106 ± 15 ng/100 ml, and TSH 3.7 ± 1.3 $\mu\text{U}/\text{ml}$. During the administration of 1 drop of SSKI twice daily for 11 days (phase II), there was a small but significant decrease in the serum concentration of T_4 and T_3 (5.8 ± 1.6 $\mu\text{g}/100$ ml and 91 ± 19 ng/100 ml, respectively) and a small but significant increase in the serum concentration of TSH (6.0 ± 3.5 $\mu\text{U}/\text{ml}$). During the administration of 5 drops of SSKI twice daily (phase III) over the following 12–19 days, these changes persisted, except for a small increase in the serum concentration of T_3 (97 ± 20 ng/100 ml), which was statistically significant when compared to values obtained during phase II. Values returned to control levels 14 days after withdrawal of SSKI. Almost all these observed changes took place within the limits of the normal range. It is postulated that, in euthyroid individuals, iodides specifically inhibit release of T_4 and probably of T_3 . The resulting slight decrease in values for serum T_4 and T_3 elicits a small increase in TSH secretion which, it is postulated, antagonizes the inhibition of hormone release induced by iodides. As a result, a new equilibrium is reached which maintains the euthyroid state.

INTRODUCTION

It seems clear that the rapid amelioration of thyrotoxicosis that iodides frequently induce in patients with

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diffuse toxic goiter results from a slowing of hormonal release. Physiological evidence that this is the case was first obtained in studies of the effect of iodides on the fractional rate of release of ^{131}I from prelabeled thyroid glands, in which a prompt slowing of ^{131}I release was induced (1–4). Since iodides enrich glandular iodine stores, however, epithyroid counting could not conclusively prove that the secretory rate of stable hormone had actually been decreased. More recent studies involving the assessment of the concomitant effects of iodide on the metabolism and concentration of endogenously and exogenously labeled hormone in serum, coupled with measurements of stable serum thyroxine (T_4)¹ concentration, have conclusively proved, however, that iodides do inhibit, at least for a time, the secretion of stable thyroxine (T_4) in patients with thyrotoxicosis (4, 5).

In the euthyroid patient, it has been much more difficult to demonstrate an effect of iodides on the rate of glandular iodine turnover or on the secretory rate for T_4 owing to the slower rate at which these processes occur. Nevertheless, Mercer, Westerink, and Adams have reported that administration of stable iodide is accompanied by a decreased rate of ^{131}I release from the prelabeled normal thyroid (6); whether iodides slow the release of stable hormone under these circumstances is uncertain, however. Evidence that they may do so has been presented in abstract form by Hollander, Nihei, Mitsuma, Scovill, and Gershengorn, who reported that in euthyroid subjects iodides induce small decreases in the serum concentrations of both stable T_4 and triiodothyronine (T_3) (7).

It is clear that if iodides do slow the release of

¹Abbreviations used in this paper: SSKI, saturated solution of potassium iodide; T_3 , triiodothyronine; T_4 , thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyrotropin.

TABLE I
Effect of Iodide Administration on Serum Thyroxine, Triiodothyronine, and Thyrotropin
Concentration in Euthyroid Subjects

Subjects	Serum T ₄				Serum T ₃				Serum TSH			
	I*	II	III	IV	I	II	III	IV	I	II	III	IV
	$\mu\text{g}/100\text{ ml}$				$\text{ng}/100\text{ ml}$				$\mu\text{U}/\text{ml}$			
1	7.8	6.0	4.7	7.3	120	106	126	120	6.9	15.3	16.0	6.4
2	6.4	4.7	4.4	6.6	125	105	110	100	3.9	3.7	5.1	3.9
3	6.9	6.3	5.6	6.9	92	68	76	90	3.7	5.4	6.0	4.3
4	8.7	7.8	7.9	—	108	95	101	—	2.8	7.3	8.8	—
5	6.0	5.0	5.5	5.8	120	108	113	115	2.5	3.1	3.6	2.4
6	5.8	6.0	5.6	5.8	90	78	90	90	4.0	5.2	3.3	2.4
7	6.4	5.0	5.3	8.0	93	86	95	110	4.9	4.8	5.8	5.2
8	10.4	8.9	—	—	113	107	—	—	3.6	6.4	—	—
9	6.3	6.1	5.6	9.0	120	110	110	120	3.0	3.4	6.9	2.4
10	3.8	3.2	3.0	4.9	85	53	58	90	2.4	5.1	3.6	3.0
Mean	6.9	5.8	5.3	6.8	106	91	97	104	3.7	6.0	6.6	3.7
SD	1.8	1.6	1.3	1.3	15	19	20	13	1.3	3.5	3.9	1.5
P value†	<0.01		<0.01		<0.01		<0.01		<0.01		<0.01	

* Phase I, mean of three values before SSKI; II, mean of last three values during administration of SSKI, 1 drop b.i.d.; III, mean of last three values during administration of SSKI, 5 drops b.i.d.; IV, value after discontinuing SSKI.

† Paired *t* test.

hormone from the normal thyroid, then there must be some mechanism whereby such an effect is overcome, since hypothyroidism rarely results from continued iodide administration in normal subjects (cf. Review, reference 8). The present studies were undertaken to attempt to ascertain whether, in normal individuals, changes in the rate of secretion of thyrotropin (TSH) play a role in the response to chronic iodide administration and the maintenance of a normal metabolic state.

METHODS

Studies were carried out in 10 euthyroid male volunteers, aged 32-84, who lived in a local noncloistered monastery. During a control period, bloods were drawn daily for 3 days (phase I). All subjects then were given 1 drop of saturated solution of potassium iodide (SSKI) twice daily for 11 days (phase II). In nine subjects, the dose of SSKI was then increased to 5 drops twice daily for a period of 12-19 days (phase III); in the remaining subject, the larger dose was not given. During the administration of SSKI, blood samples were obtained approximately every other day. In 8 of the 10 subjects, blood was also obtained 14 days after SSKI had been discontinued (phase IV). All samples of blood were drawn at approximately 5:00 p.m.

Serum samples were analyzed for T₄ concentration in duplicate by a competitive protein-binding assay (normal range, 4-11 μg T₄/100 ml) (9) and in triplicate for TSH concentration by radioimmunoassay (normal range, 0-9 μU /ml) (10). Analyses for serum triiodothyronine (T₃) concentration were also performed in triplicate by radioimmunoassay using a method developed in our laboratory in which T₃ is extracted from the test serum and from T₃-enriched

serum standards prior to assay.² For each test, samples from each subject were assayed concurrently. Since the changes in serum T₄, T₃, and TSH concentrations induced by iodide administration were small, the data for each test were evaluated by utilizing the mean values obtained during the control period (3 days) and those present in the last three serum samples obtained during the two periods of iodide administration. Total iodide concentration was measured in one sample from each phase in all patients by a colorimetric method.³ Statistical analyses (paired *t* test) were carried out as described by Snedecor and Cochran (11).

RESULTS

Results of the study are shown in Table I.

Serum T₄ concentration. Control values for the serum T₄ concentration were within the normal range in all subjects, averaging 6.9 ± 1.8 $\mu\text{g}/100\text{ ml}$ (mean $\pm$ SD). During the administration of the lower dose of SSKI (phase II), serum T₄ decreased in 9 of 10 subjects. Mean value for the entire group during this period was 5.8 ± 1.6 $\mu\text{g}/100\text{ ml}$, and the change from control values was statistically significant ($P < 0.01$). Serum T₄ concentration did not display a further significant decrease during the administration of the larger dose of SSKI (phase III), although the mean

² In this method, antiserum was kindly supplied by Doctors Hockert, Mayberry, and Gharib of the Mayo Clinic. Normal values have averaged 96 ± 15 ng/100 ml (mean $\pm$ SD) in 40 subjects. Burger, A., A. Moore, and S. H. Ingbar. Manuscript in preparation.

³ Performed at the Boston Medical Laboratory, Waltham, Mass.

value decreased to $5.3 \pm 1.3 \mu\text{g}/100 \text{ ml}$. In samples obtained following withdrawal of iodides, mean serum T_4 concentration had returned almost exactly to the control value ($6.8 \pm 1.3 \mu\text{g}/100 \text{ ml}$). All values for serum T_4 concentration remained within the normal range throughout the study, except in subject 10, in whom the control value was marginally low ($3.8 \mu\text{g}/100 \text{ ml}$). In this patient, the serum T_4 concentration decreased to $3.2 \mu\text{g}/100 \text{ ml}$ during phase II and 3.0 during phase III. No evidence of intrinsic thyroid disease could be obtained in this patient, since control values for serum free T_4 , total serum T_3 , and TSH concentrations were normal, and analyses for antithyroid antibodies (tanned red cell agglutinins) were negative.

Serum iodide concentration. Mean value for total serum iodide concentration (total iodine minus T_4 -iodine) was $1.1 \pm 0.6 \mu\text{g}/100 \text{ ml}$ during the control period (phase I) and increased markedly during phase II ($134 \pm 123 \mu\text{g}/100 \text{ ml}$). Values rose further during phase III ($552 \pm 247 \mu\text{g}/100 \text{ ml}$) and returned almost to control values during phase IV ($2.7 \pm 0.7 \mu\text{g}/100 \text{ ml}$).

Serum T_3 concentration. Control values for serum T_3 concentration were normal in all subjects, ranging between 85 and $125 \text{ ng}/100 \text{ ml}$, and averaging 106 ± 15 . During phase II, serum T_3 decreased in all subjects, the mean of $91 \pm 19 \text{ ng}/100 \text{ ml}$ being significantly lower than the control mean ($P < 0.01$). During phase III, in eight of nine subjects, serum T_3 concentration increased from values obtained in phase II; in the remaining subject, it was unchanged. For the group as a whole, values averaged $97 \pm 20 \text{ ng}/100 \text{ ml}$. This increase was highly significant when values were compared with those obtained during phase II ($P < 0.01$), but values remained significantly lower than control values ($P < 0.05$). After iodide withdrawal, serum T_3 concentrations returned to control values ($104 \pm 13 \text{ ng}/100 \text{ ml}$). All values for serum T_3 remained within the normal range throughout the study.

Serum TSH concentration. Serum TSH concentration was normal in all subjects ($3.7 \pm 1.3 \mu\text{U}/\text{ml}$) before iodide administration. During phase II, serum TSH concentration increased in 8 of 10 subjects, values for the entire group averaging $6.0 \pm 3.5 \mu\text{U}/\text{ml}$ ($P < 0.01$ vs. control period). During phase III, serum TSH increased further in six of nine subjects and values for the entire group averaged $6.6 \mu\text{U}/\text{ml}$. Values obtained during phase III were significantly increased in relation to control values ($P < 0.01$), but not in relation to those obtained during phase II. After withdrawal of iodides, serum TSH concentrations returned to their control level ($3.7 \pm 1.5 \mu\text{U}/\text{ml}$). Except in one subject, in whom serum TSH increased to 15.3 and $16.0 \mu\text{U}/\text{ml}$ during the two periods of iodide administration, values for serum TSH remained within the normal range in

FIGURE 1 Sequential values for serum concentrations of T_3 , T_4 , and TSH in patient 3 during each phase of treatment. Serum TSH concentrations were assayed on 2 separate days and values for each assay are plotted separately.

all subjects throughout the study. The sensitivity and reproducibility of the TSH assay is demonstrated by the similarity of the TSH assay curves in subject 3, in whom the assay was carried out on 2 different days (Fig. 1).

DISCUSSION

The present studies have demonstrated that the administration of large doses of iodide (72 and 360 mg daily) to euthyroid subjects for periods as long as 39 days results in small, but highly significant, decreases in the serum concentration of T_4 and T_3 . Since iodide administration does not effect the peripheral turnover of T_4 in hyperthyroid ($5, 12$) or euthyroid⁴ subjects, it seems unlikely that the present observations can be explained on the basis of changes in the peripheral metabolism of the thyroid hormones. For two reasons, it seems likely that such decreases reflect an inhibition of hormonal secretion, rather than synthesis, particularly in the case of T_4 . First, even large doses of antithyroid agents decrease the serum protein-bound iodine concentration little, if at all, during comparable periods of administration (10). Second, any inhibition of hormonal synthesis that iodide

⁴ Wartofsky, L., and S. H. Ingbar. Unpublished observations.

may have induced (acute Wolff-Chaikoff effect) would have been expected to be transient in these normal subjects (13). In the case of T_3 , some of the initial decline may have reflected decreased generation of T_3 from T_4 (14), secondary to a decrease in serum T_4 concentration.

The design of the present experiments does not permit a conclusive judgement that serum T_4 and T_3 concentrations had ceased to decline by the time that iodides were withdrawn. Nevertheless, as compared to values found during phase II, serum T_4 concentration declined only slightly and insignificantly during phase III, while serum T_3 concentrations actually increased, though not to normal. Thus, it seems likely that had the duration of iodide administration been even greater, values for serum T_4 and T_3 would have remained within the normal range. This supposition is consonant with the clinical observation that iodides rarely, if ever, induce manifest hypothyroidism in normal individuals (8). The present data suggest that such stabilization of hormonal secretion and plasma concentration during continued iodide administration may be the result of slight enhancement of TSH secretion, in view of the consistent and continued increases in serum TSH concentration that occurred during treatment periods. This interpretation is consonant with the data of Greer and DeGroot, who demonstrated dose-related antagonism in the respective stimulatory and inhibitory effects of TSH and iodide on thyroidal ^{131}I release rates (3). Enhanced secretion of TSH may also explain the rise toward normal in serum T_3 that occurred during phase III, in view of evidence that hypersecretion of TSH may favor the secretion of T_3 relative to T_4 (15).

The present results are somewhat at variance with those obtained by other workers. In the preliminary report of Hollander and co-workers, TSH values were said not to have been increased during iodide administration, even though both T_4 and T_3 concentrations in serum were decreased (7). Similarly, Sawin, Hershman, Handler, and Utiger failed to note an increase in serum TSH concentration in patients given very large doses of iodide together with high doses of methimazole for 3 wk (16). Hall, Amos, and Ormston have reported that when a sensitive assay is employed, serum TSH rises within a week after initiation of treatment with iodide and carbimazole (17). Earlier, the same workers had failed to detect an increase in serum TSH by a less sensitive assay method when carbimazole alone was given. Hence, it is unclear whether the positive results obtained by these workers were due to the more sensitive assay or to the addition of iodide. It seems likely that the present positive results were made evident by several factors, including sensitivity and reproducibility of the TSH assay, the multiple samples analyzed during each treatment period, and the analysis of all samples from a given

patient in the same assay. The sensitivity and reproducibility of the assay that we employed, and hence its ability to detect significant changes in serum TSH within the normal range, is demonstrated by the similarity of the patterns of response of serum TSH to iodide in two patients whose samples were analyzed on two separate occasions. As shown in Fig. 1 for patient 3, confirmation of the pattern of TSH response was obtained.

Snyder and Utiger have reported that very slight changes in the dosage of thyroid hormone given to normal and hypothyroid individuals can produce pronounced effects on pituitary responsiveness to TSH-releasing hormone (TRH) (18). In this context, it is noteworthy that, with rare exception, all of the changes in serum T_4 , T_3 , and TSH concentration that we observed in the present study took place within the normal range. These findings emphasize the extent to which feedback control of TSH secretion is finely attuned to slight changes in hormonal availability.

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