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^{35}S-ANTITHYROID DRUG CONCENTRATION AND ORGANIC BINDING OF IODINE IN THE HUMAN THYROID

J. H. LAZARUS, B. MARCHANT, W. D. ALEXANDER AND D. H. CLARK

Department of Medicine, Western Infirmary, Glasgow

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SUMMARY

^{35}S-methimazole (MMI), ^{35}S-carbimazole or ^{35}S-propylthiouracil (PTU) were given orally to fifty-five patients at various times up to 12 h before surgical thyroidectomy. The amount of ^{35}S radioactivity and labelled drug in thyroid and plasma samples was measured. Intrathyroidal inhibition of organic binding of iodine by MMI, carbimazole and PTU was measured after intravenous administration of ^{131}I, ^{132}I or ^{125}I-iodide. After administration of ^{35}S-carbimazole or ^{35}S-MMI the thyroid to serum (T/S) ratio of ^{35}S radioactivity was greater in thyrotoxic glands than in non-toxic adenoma tissue. ^{35}S-MMI was found in thyroid and plasma samples after administration of ^{35}S-carbimazole. The T/S ^{35}S-MMI was greater than 1 in most but not all patients. ^{35}S radioactivity was also concentrated in the thyroid after administration of ^{35}S-PTU. In thyrotoxic glands there was an 80% inhibition of iodine organification in patients receiving MMI and 60% for those receiving PTU. It is suggested that carbimazole and MMI can be given once or twice daily in some patients but PTU would be less suitable for this dose schedule.

Drug treatment of thyrotoxicosis using the thiocarbamide group of antithyroid drugs renders patients euthyroid after a variable period of administration. This variation in response may reflect individual differences, either in the nature of the disease process or in the response to antithyroid drugs.

In this study we examine thyroidal levels of the thiocarbamide antithyroid drugs in thyrotoxicosis, non-toxic goitre and 'normal' thyroid glands with particular emphasis on quantifying the effect of the drugs on inhibiting the organic binding of iodine within the gland.

MATERIALS, METHODS AND PATIENTS

Materials

^{35}S-labelled propylthiouracil (PTU), methimazole (MMI) and carbimazole were obtained

Correspondence: Dr J. H. Lazarus, Department of Medicine, University Hospital of Wales, Heath Park, Cardiff CF4 4XN.

from the Radiochemical Centre, Amersham, at a specific radioactivity of 32·0–46·1 mCi/mmol, 38·2 mCi/mmol and 28·2 mCi/mmol respectively. All the compounds were greater than 97% radiochemically pure by thin-layer chromatography, and infra-red spectroscopy confirmed the material to be chemically pure. ^{132}I, ^{131}I and ^{125}I iodine (carrier free) were also obtained from the Radiochemical Centre, Amersham.

Methods

Quantitation of the total ^{35}S radioactivity and the unmetabolized ^{35}S-antithyroid drug in the thyroid and serum samples was performed as previously described (Marchant & Alexander, 1972). The duration of inhibition of organic binding of iodine after administration of carbimazole, MMI or PTU was measured by trichloroacetic acid precipitation using the method of Alexander & Wolff (1966). The statistical test used was the Wilcoxon rank test (Documenta Geigy, 1970).

Patients

Fifty-five patients undergoing thyroidectomy were studied. Thirty patients had Graves' disease, sixteen were operated on for non-toxic goitre and 'normal' thyroid tissue was obtained in eleven patients. Some of these eleven patients also had operations for non-toxic goitre. Thyroid status was evaluated by $PB^{127}I$ (Technicon), T3 resin uptake (Abbott), free thyroxine index and 5 and 48 h ^{131}I uptake where appropriate. Thyrotoxic patients were maintained on carbimazole or methimazole 10 mg q.d.s. or propylthiouracil 100 mg q.d.s. together with triiodothyronine 20 μg q.d.s. before surgery and were euthyroid at the time of operation. Thyrotoxic patients had been maintained on antithyroid drugs and T3 for 3–15 months before surgery. Patients with non-toxic goitre or thyroid neoplasms received no maintenance drug therapy. A single oral dose of 10 mg MMI or carbimazole or 100 mg PTU each containing 100 μCi ^{35}S-labelled antithyroid drug was given 4, 8 or 12 h before excision of the gland. Those patients in whom the duration of inhibition of organic binding of iodine was measured, received 5 μCi ^{131}I or ^{132}I-iodide intravenously 1 h prior to gland excision. ^{125}I-iodide was used in three patients. Thyroid glands were collected on ice and samples were obtained for analysis and histological examination. 'Normal' thyroid tissue was obtained from the area surrounding an adenoma or tumour. The nature of all samples analysed was verified by subjecting an immediate adjacent portion of tissue to histological examination. This confirmed that the histology of the thyrotoxic glands was consistent with that of drug treated Graves' disease in every case; the non-toxic goitres were all follicular adenomas and the 'normal' tissue did not contain any nodules or large amounts of lymphoid infiltration. Venous blood samples were taken at the time of gland excision.

RESULTS

Carbimazole/methimazole

The serum level of ^{35}S radioactivity ranged between 0·00054 and 0·0048% dose/ml. There was no difference in serum ^{35}S-radioactivity between the groups at 4, 8 or 12 h following administration of labelled drug. ^{35}S radioactivity accumulated in most of the thyroid glands (Table 1); the maximum concentration of 0·040% dose/g thyroid was attained in a 'normal' piece of tissue. The mean ^{35}S radioactivity in thyrotoxic glands 8 h after ^{35}S drug administration (0·0074% dose/g) was significantly greater than the mean ^{35}S radioactivity in

adenomas of 0·0038% ($P<0·01$). Values in 'normal' tissue at this time ranged from 0·0023 to 0·040% dose/g.

8 h after radioactive drug administration the thyroid to serum (T/S) ratio of ^{35}S radioactivity in the thyrotoxic patients was significantly greater than that seen in the patients with non-toxic goitre ($P<0·05$). This trend was also observed 12 h after administration of ^{35}S drug.

TABLE 1. Concentration of ^{35}S radioactivity in the thyroid gland of patients receiving ^{35}S carbimazole or ^{35}S methimazole

Histological diagnosis	Time* (h)	No. of patients	^{35}S% dose/g		Thyroid/serum ^{35}S
			Mean	Range	
Thyrotoxic	4	7	0·0097	0·0044–0·014	2·6 (1·4–3·3)
Thyrotoxic	8	15	0·0074	0·0022–0·013	3·4 (0·9–6·6)
Thyrotoxic	12	3	0·016	0·0110–0·025	6·3 (6·2–6·3)
'Normal'	4	3	0·0083	0·0051–0·011	3·0 (1·7–3·6)
'Normal'	8	5	0·011	0·0023–0·040	5·5 (1·4–12·4)
'Normal'	12	1	0·010	—	6·2 —
Non-toxic goitre	4	2	0·0029	—	0·83 —
Non-toxic goitre	8	6	0·0038	0·0014–0·0073	1·9 (0·8–3·3)
Non-toxic goitre	12	3	0·0080	0·0033–0·010	4·4 (2·0–6·2)

* Refers to time of drug administration before thyroid excision.

TABLE 2. Thyroid/serum ratio of ^{35}S methimazole following administration of carbimazole or methimazole

Time*	Normal			Non-toxic goitre			Thyrotoxic		
(h)	*n*	Mean	Range	*n*	Mean	Range	*n*	Mean	Range
4	3	1·4	0·9–2·2	—	—	—	2	1·2	0·9–1·5
8	4	3·6	0·5–10·0	3	1·6	1·2–1·8	13	1·4	0·7–2·5
12	1	2·0		2	2·3	2·0–2·7	—	—	—

— Data not available.

* Refers to time of drug administration before thyroid excision.

No unmetabolized carbimazole was found in the serum or tissue extracts of any of the patients receiving carbimazole, but methimazole was demonstrated in every case (Marchant *et al.*, 1972). The T/S ratios of unmetabolized methimazole in the different thyroid tissue specimens are shown in Table 2. No significant difference in T/S ratio was noted between 'normal', adenomatous or toxic glands. In several instances, including four patients with thyrotoxicosis, a T/S ratio of less than 1 was found. The high mean value in 'normals' at 8 h is due to a single high T/S ratio of 10·0 observed in the 'normal' tissue from a patient with a thyroid adenoma.

Inhibition of iodide organification 8 h after administration of ^{35}S-labelled carbimazole or methimazole was measured in eleven thyrotoxic subjects (Table 3) and in 'normal' thyroid tissue from four euthyroid patients who had received ^{35}S drug between 8 and 12 h prior to gland excision.

Inhibition of iodide organification was over 90% in normal tissue and in eight thyrotoxic glands ranged from 86·8% to 98·8%. In three patients the inhibition was lower; this is discussed below.

TABLE 3. Inhibition of thyroid hormone biosynthesis in thyroid glands from thyrotoxic patients and from patients with normal thyroid tissue

Histological diagnosis	% inhibition of iodide organification	T/S ^{35}S	T/S methimazole	Time on drug* (months)
T†	98·8	2·4	—	15
T†	98·0	6·6	—	6
T†	96·0	5·6	2·5	12
T†	95·2	3·6	1·7	12
T†	95·0	4·2	2·3	12
T†	94·9	3·0	0·7	3
T†	90·5	2·5	1·2	33
T†	86·8	2·2	1·9	60
T†	57·0	1·9	0·9	18
T†	42·7	5·9	1·7	3
T†	35·7	3·5	1·4	12
N†	95·2	1·4	0·4	—
N†	93·7	2·8	1·7	—
N‡	91·4	5·0	2·0	—
N‡	90·3	6·2	2·0	—

T = Thyrotoxic tissue: patient euthyroid on drugs at time of operation.
N = 'Normal' thyroid tissue.

* Time on carbimazole or methimazole before operation.
† Received ^{35}S-labelled drug 8 h before gland excision.
‡ Received ^{35}S-labelled drug 12 h before gland excision.

Propylthiouracil

The serum level of ^{35}S radioactivity ranged between 0·00047 and 0·0055% dose/ml. The concentration of activity in the thyroid is shown in Table 4. As there was no unmetabolized drug in the serum at later time intervals no T/S values are available but free PTU was found in the thyroid gland at later time intervals. The T/S ^{35}S ratios increased in relation to the time interval after administration, the highest being noted in a patient with non-toxic goitre 8 h after receiving the drug. In general the T/S ^{35}S ratios were higher than those observed for methimazole partly because serum ^{35}S radioactivity at later time intervals tended to decrease more rapidly after ^{35}S PTU compared to ^{35}S MMI.

Inhibition of iodide organification was measured in one normal gland (72%) and the values in two thyrotoxic patients were 57% and 62% 8 h after ^{35}S PTU administration with a 100 mg stable carrier dose (see Marchant *et al.*, 1971a).

TABLE 4. Thyroidal accumulation of ^{35}S radioactivity at varying times after administration of ^{35}S-propylthiouracil

Histological diagnosis	Time* (h)	^{35}S% dose/g	Thyroid/serum ^{35}S	Thyroid/serum propylthiouracil
Thyrotoxic	2	0·0105	3·0	
Thyrotoxic	2	0·0088	1·6	
Thyrotoxic	5	0·0034	3·3	7·4
Thyrotoxic	8	0·0110	16·0	
Thyrotoxic	8	0·0139	20·5	
'Normal'	8	0·0167	13·4	
'Normal'	8	0·0053	7·1	
Non-toxic goitre	2	0·0032	1·0	
Non-toxic goitre	4	0·0080	4·0	
Non-toxic goitre	4	0·0136	6·1	
Non-toxic goitre	4	0·0096	3·8	7·0
Non-toxic goitre	8	0·0275	59·5	

* Refers to time of drug administration before thyroid excision.

DISCUSSION

These studies confirm and extend the previous reports of thyroidal accumulation of ^{35}S radioactivity following administration of carbimazole, methimazole or propylthiouracil to humans (Marchant *et al.*, 1972) and provide the first data on the efficiency of blocking of thyroid hormone synthesis *in vivo* by a thiocarbamide in relation to its thyroidal drug concentration.

There was considerable variation in accumulation of radioactivity (as measured by T/S ^{35}S ratio) in different histological types of gland. It was not possible to quantify the metabolites in the present studies because of the small dose of administered radioactivity. There was no correlation, however, between ^{35}S concentration and the degree of inhibition of thyroxine biosynthesis (Table 3). The T/S ratios of MMI found in the human thyroid were low, indicating marked differences from those observed in rats (Marchant & Alexander, 1972).

Carbimazole and MMI were equally effective in 10 mg doses, producing more than 90% inhibition of organification 12 h after administration of a single dose in euthyroid subjects. Almost complete inhibition of organification was found 8 h after a 10 mg dose of MMI in five thyrotoxic subjects. It should be noted that thyrotoxic patients were receiving long-term treatment with carbimazole and triiodothyronine whereas patients providing 'normal' tissue were not. However, the results showed that the dosage regimen used in the treatment of thyrotoxicosis was effective in blocking thyroid hormone synthesis.

^{35}S studies in the subjects given 100 mg PTU showed that partial inhibition of organification occurred in these patients with absence of detectable unmetabolized drug in the serum. However, PTU was found in the thyroid indicating that the thyroidal level of drug was a more important index than the serum level in determining the duration of action of this compound (Marchant *et al.*, 1971a).

In contrast to carbimazole, a single 100 mg dose of PTU produced only 72% inhibition of organification 7 h after the dose in one euthyroid subject and 57–62% inhibition 8 h after the

dose in two thyrotoxic subjects receiving long-term treatment with PTU and triiodothyronine.

The results of the inhibition studies showed that in the doses used, MMI was more effective than PTU in inhibiting organification of iodine. This is consistent with previous work (Stanley & Astwood, 1947) which suggested that the duration of action of a single 5 mg dose of MMI was 'nearly 24 h' and that 500 mg doses of PTU had only a short duration of action.

It was noted that two of the three patients with low inhibition of iodide organification were 'clinically resistant' to the drugs. No explanation was found for this in this study but it is known that other factors, such as long-term treatment with methimazole or PTU (Pharmakiotis & Alexander, 1974) and phenobarbitone (Lees & Alexander, 1974), influence the metabolism of these drugs in rats. Furthermore, the level of the thyroidal iodine stores also affects the rate of antithyroid drug metabolism (Marchant *et al.*, 1971b).

The reduced potency of PTU in man may be due to differences in the metabolism of carbimazole and methimazole compared to propylthiouracil, as suggested by studies in the rat (Pittman *et al.*, 1971; Marchant & Alexander, 1972; Sitar & Thornhill, 1972, 1973). There is also evidence that although both PTU (Kampmann *et al.*, 1974) and methimazole (Shimmins *et al.*, 1969; Pittman *et al.*, 1971) are rapidly absorbed after oral administration, the plasma half-life and whole body retention of methimazole is significantly longer than that of PTU (Marchant, 1971). The rapid elimination of PTU from the plasma into the urine as the conjugate PTU glucuronide may explain the relatively short action of the drug compared to MMI (Marchant, 1971; Marchant *et al.*, 1971a). A similar suggestion was made by McGinty *et al.* (1948), who proposed that the inactivity of benzylthiouracil in man was due to its complete conjugation, so that the partial conjugation of PTU could explain its relatively low potency in man. It is interesting to note, however, that PTU is a highly effective anti-thyroid compound in rats with a potency 100 times that of thiourea *in vivo* (Astwood *et al.*, 1945).

The PTU glucuronide exists as a minor compound in the plasma of rats but is the major compound in man; thus the species difference in potency of PTU may possibly be explained by different conjugating abilities for PTU in rats and man (Marchant, 1971).

These metabolic differences may effect therapeutic recommendations about the dose and frequency of the drugs. The usual advice is for the drugs to be administered three or four times during a 24 h period (Goodman & Gilman, 1970). However, Greer *et al.* (1965) reported a group of hyperthyroid patients in whom it appeared that a single daily dose of PTU was adequate. Barnes & Bledsoe (1972) suggested use of a perchlorate discharge to predict the desired frequency of dose of antithyroid drugs. The present study has shown that for most patients receiving carbimazole or methimazole inhibition of thyroid hormone biosynthesis is high up to 8 h after administration. This implies that administration of the drugs more than three times per day is unnecessary. It would appear that in many patients the drugs could be given once or twice daily and still maintain a euthyroid state. In contrast, the present data in relation to the inhibitory effects of PTU on hormone biosynthesis suggests that this drug would be less suitable for once daily administration as suggested by Greer *et al.* (1965). Further, it has been shown that, for the doses used in the preoperative preparation of thyrotoxic patients in this study, methimazole or carbimazole produced a greater degree of inhibition of hormone biosynthesis than the equivalent maintenance dose of propylthiouracil. This is consistent with the retrospective analysis of Barnes & Bledsoe (1972) who

showed that methimazole was more effective than PTU in achieving control on a less frequent dose schedule.

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