Brazilian J Med Biol Res (1986) 19: 723-729

STANDARD DOSE ^{131}I THERAPY FOR TOXIC MULTINODULAR GOITER IN AN ENDEMIC GOITER REGION

E. GONÇALVES, J.A.S. CASTRO and J.L. GROSS

Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre, 90000 Porto Alegre, RS, Brasil

1. The effect of the standard 15 mCi dose of ^{131}I on the thyroid function of 25 patients from an endemic goiter region with toxic multinodular goiter of different sizes was determined.

2. The patients were followed for 1 to 5 years and 7 months (mean: 2 years and 10 months). Eighteen patients were treated with the antithyroid drugs propylthiouracil or methimazole before ^{131}I and seven only received ^{131}I.

3. All but three patients achieved euthyroidism after a single dose of ^{131}I. Two patients in the antithyroid treatment group became hypothyroid 2 months and 2 years after the isotope therapy, respectively. Pretreatment with antithyroid drugs did not significantly modify the effectiveness of ^{131}I treatment.

4. This simplified dose regimen of ^{131}I was effective in the treatment of hyperthyroidism caused by multinodular goiter in an endemic region, and the efficacy was independent of the size of the goiter.

Key words: toxic multinodular goiter, ^{131}I therapy, thyrotoxicosis.

Introduction

In iodine-deficient areas there is an increase in the prevalence of thyrotoxicosis caused by multinodular goiter (Pendergrast *et al.*, 1961). Southern Brazil is an endemic goiter region, where the prevalence of the condition can reach up to 30% (Sampaio, 1972). A survey of this population disclosed that nodular goiter was the cause of thyrotoxicosis in 53% of the patients (Gross *et al.*, 1983) and in some cases it can assume dramatic proportions (Kruter *et al.*, 1982).

There is no general agreement as to the best therapeutic option under these circumstances. Thyroidectomy is effective, but there is some morbidity which can be higher in the patients with toxic multinodular goiter (TMNG) because they are usually older and may have associated illnesses. The therapeutic effect of radioactive iodine is considered rather slow and requires large doses of 50 to 75 mCi (Miller, 1978), which calls for hospitalization of the patient (NCRP, 1970). Furthermore treatment with ^{131}I can be followed by thyroid storm (Aach and Kissane, 1972). Ng Tang Fui and Maisey (1979) reported that lower doses of ^{131}I can also be effective in the treatment of TMNG.

There are divergent opinions about the method of calculating the appropriate ^{131}I dose. Studer *et al.* (1985), on the basis of the heterogeneity of hormone production by the follicles of TMNG patients, support the view that any dose calculation is irrelevant.

The present study was undertaken in order to evaluate the effectiveness of a standard 15 mCi dose regimen of ^{131}I and to determine if previous treatment with antithyroid drugs

Correspondence: Dr. J.L. Gross, Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, 90000 Porto Alegre, RS, Brasil.

modifies the therapeutic response to ^{131}I in patients with TMNG in an endemic region.

Patients and Methods

A total of 25 patients with obvious TMNG upon clinical examination were treated with 15 mCi ^{131}I at the Hospital de Clínicas de Porto Alegre between 1980 and 1984. These patients came from several regions of Rio Grande do Sul where the prevalence of goiter may reach up to 30% (Sampaio, 1972). The history of each patient was taken and each was submitted to physical examination and to the estimation of goiter size (Table 1). None of them had typical findings of Graves' disease nor a history of iodine ingestion that may have caused Jod-Basedow disease. The diagnosis of thyrotoxicosis was also based on measurements of total serum thyroxine (T4), total triiodothyronine (T3) and 24-h ^{131}I uptake. T4 and T3 were determined by radioimmunoassay utilizing commercial kits (Trilab, São Paulo, Brazil). The values for normal individuals from the same region were: T4, 5.0 to 11.5 μg/dl; T3, 70 to 275 ng/dl; 24-h ^{131}I uptake, 21 to 63% (Gross *et al.*, 1983). Patients with one laboratory value within the normal range were also submitted to the T3 suppression test (25 μg TID for 10 days) or the TRH test (200 μg intravenous). The thyroid was considered suppressible when the 24-h ^{131}I uptake fell to less than 50% of the basal value (Burke, 1967). The absence of the normal increase of TSH after TRH administration was considered compatible with the diagnosis of thyrotoxicosis. The normal response to TRH was also previously established (Schneider *et al.*, 1985). TSH was measured with a commercial radioimmunoassay kit (Diagnostic Product Corporation, California, USA) and the normal plasma range was 0-6.5 uUI/ml. The thyroid scintigrams were performed 24 h after the ingestion of 100 μCi of ^{131}I using a gamma camera (Ohio Nuclear Series 100). The pretreatment scintigraphic patterns of TMNG were classified as follows: *a*: radioisotope uptake restricted to one area which may or may not correspond to a palpable nodule; *b*: discrete radioisotope uptake in two or more areas with little or no uptake by the rest of the gland; *c*: irregular uptake throughout the gland. Antimicrosomal thyroid antibodies were measured by the hemmaglutination technique (SERA-TEK, Ames, Laboratório Miles do Brasil, Ltda.).

Sixteen patients received propylthiouracyl (PTU) and two patients methimazole (MTZ) before the ^{131}I treatment. They formed the Pretreatment Group. Two other patients used the antithyroid drugs so irregularly that the amount could not be estimated. The average daily dose of PTU in 15 patients before ^{131}I treatment was 362 mg, varying from 100 to 600 mg. The length of antithyroid treatment before ^{131}I treatment varied from 2 to 36 months, with an average of 8.6 months. The daily average dose and the length of antithyroid treatment before ^{131}I are indicated in Table 1. The antithyroid drugs were stopped three days before and resumed three days after the administration of ^{131}I. Seven patients did not receive antithyroid drugs before ^{131}I and they are denoted the No Treatment Group. The two groups were similar in relation to age and goiter size and both included several patients with serious associated clinical conditions (Table 1). However, in the Pretreatment Group there were 4 males but the No Treatment Group was composed of females only. Both groups were also similar in relation to the scintigraphic patterns, 24-h ^{131}I uptake and to the T4 and T3 values (Table 2). Antimicrosomal antibodies were positive in three of the 18 patients in the Pretreatment Group. The test for these antibodies was negative for 4 of 7 patients in the No Treatment Group but not available for the remaining three patients in this group (Table 2).

All patients were followed regularly after ^{131}I treatment both clinically and with measurements of T4 and T3. The effectiveness of treatment was determined when the patients had been off the antithyroid drug for at least one month. Plasma TSH was measured regularly when clinically indicated or when T4 levels fell to or below the lower limit of the normal range. Plasma TSH values greater than 13 mIU/ml were considered diagnostic of hypothyroidism.

Statistical analysis was performed using the

Table 1 - *Clinical characteristics, anti-thyroid drug dosage and associated conditions of toxic multinodular goiter patients.*

Patient no.	Patient identification	Age	Sex	Goiter size (grams)	ATD dosage		Associated conditions
					Mean (mg/day)	Duration (months)	
01	RV	36	F	90	480	2.5	iron deficiency anemia
02	MS	81	F	50	PTU	irregular use	
03	MC	57	F	70	262	4	obesity - lost 7 kg before test
04	MSR	65	M	80	300	36	diabetes - atrial fibrillation
05	AM	60	F	80	300	9	tested while on PTU
06	BSP	59	F	200	600	3	atrial fibrillation
07	LMS	48	F	150	400	2	---
08	COG	49	F	80		24	---
09	AMB	51	F	60	300	6	diabetes, hypertension, on propranolol
10	HSD	51	F	80	370	6	hypertension, on propranolol
11	AHH	55	F	60	600	4	hypertension, ischemic heart disease
12	AVS	55	M	80	500	15	pleural effusion etiology?
13	IND	65	F	120	300	4	diabetes, hypertension
14	DR	64	M	substernal	MTZ	irregular use	---
15	ONFC	61	F	150	400	5	ischemic heart disease, on propranolol
16	CM	61	F	50	160	7	hypertension, on propranolol
17	MRC	50	F	80	230	6	
18	CMMM	51	M	60	230	5	thyphoid fever
	Mean ± SD	56.6 ± 9.5		91 ± 41	362 ± 134	8.7 ± 9.1	
19	EMR	78	F	40	–	–	migraine, on propranolol
20	EMF	56	F	60	–	–	ischemic heart disease, on propranolol
21	FRG	46	F	200	–	–	---
22	IBCR	45	F	80	–	–	hypertension, on propranolol
23	MERS	78	F	50	–	–	chronic obstructive pulmonary disease
24	OGG	60	F	200	–	–	pneumonia
25	HK	74	F	substernal	–	–	lactose intolerance
	Mean ± SD	62.4 ± 14.4		105 ± 74			

Table 2 - *Laboratory data of toxic multinodular goiter patients before treatment with ^{131}I.*

The scintigraphic pattern is defined in the Patients and Methods Section. *Negative T3 suppression test; NT, not tested; flat TRH test.

	Identification	Scintigraphic pattern	^{131}I Uptake (%)	T4 (μg/dl)	T3 (ng/dl)	Antimicrossomal antibodies
01	RV	b	41	19.0	305	Neg.
02	MS	c	38	14.5	415	NT
03	MC	a	66	14.2	265	Neg.
04	MSR	c	–	16.2	210	Neg.
05	AM	c	62	15.8	318	Neg.
06	BSP	a	22	18.8	350	Neg.
07	LMS	c	42	20.5	236	Neg.
08	COG	a	57	16.2	325	1:6400
09	AMB*	c	39	11.2	290	Neg.
10	HSD	c	81	24.0	340	Neg.
11	AHH	c	67	16.0	500	Neg.
12	AVS	b	33	20.0	365	Neg.
13	IHD	c	14	14.2	290	1:1600
14	DR	c	72	15.0	350	Neg.
15	OMFC	c	96	32.0	–	Neg.
16	VM	b	62	19.8	440	Neg.
17	MKC*	c	85	17.0	260	Neg.
18	CMMM	a	100	14.5	200	1:400
	Mean ± SD		58 ± 25.0	17.7 ± 4.7	321.1 ± 80.0	
19	EMR	a	17	13.4	345	Neg.
20	EM*	b	30	14.6	210	Neg.
21	FRG	a	41	15.7	228	NT
22	IBCR	c	46	18.8	187	NT
23	MERS	c	38	14.2	415	NT
24	OGG*	a	87	12.0	162	Neg.
25	HR	a	11	12.5	204	Neg.
	Mean ± SD		38 ± 25.0	14.5 ± 2.3	250 ± 93	

unpaired Student *t*-test, with the level of significance set at 5%.

Results

Before treatment the mean level of T4 was 16.6 μg/dl and T3 was 286.8 ng/dl. These results were significantly above the normal range for our normal population ($P < 0.001$). The mean 24-h ^{131}I uptake was 46.5% and therefore, within our normal range. Serum T4 was more useful than T3 to establish the diagnosis of thyrotoxicosis. Only one patient had T4 level within the normal range, while 10 patients had T3 levels in the range of our normal population (Table 2). Eight of these 10 patients had clinical problems that may have accounted for the T3 values being within normal limits (Table 1). The was no correlation between serum T4 and T3 levels and goiter size.

Table 3 shows the laboratory and follow-up findings for the 25 patients with TMNG treated with ^{131}I. Mean post-treatment T4 was 8.7 μg/dl and T3 was 152 μg/dl. The T4 and T3 data shown in Table 3 were obtained when the patients were off the antithyroid medication and considered to be in euthyroid status. The time to reach euthyroidism is indicated in the Table for each individual. Seventeen patients reached euthyroidism within 6 months after ^{131}I treatment. Only three patients needed more than 1 year to reach euthyroidism and they belonged to the Pretreatment Group. Two of these received an additional dose of ^{131}I to control the disease. One patient in the No Treatment Group also needed an extra ^{131}I dose. Two patients from the Pretreatment Group progressed to hypothyroidism 2 months and 2 years after the ^{131}I treatment. The time to reach euthyroidism was shorter in the No Treatment Group but the difference was not statistically significant ($0.05 < P < 0.07$). The last follow-up evaluation when serum T4 and T3 levels were obtained is also indicated in Table 3. The average follow-up period for all patients was 2 years and 10 months, with no differences between the two groups.

Table 3 - *Laboratory data, time to reach euthyroidism and follow-up period of toxic multinodular goiter patients after ^{131}I treatment.*

Patient no.	Patient identification	T4 (μg/dl)	T3 (ng/dl)	Time to reach euthyroidism (months)	Follow-up period (months)
01	RV	6.6	175	2	25
02	MS	2.0	–	–	hypothyroid 2 months after ^{131}I
03	MC	5.5	160	6	42
04	MSR	7.1	135	39	45
05	AM	8.7	188	4	46
06	BSP	10.4	240	3	22
07	LMS	6.9	123	3	36
08	COG	6.7	–	12	26
09	AMB	5.0	120	6	hypothyroid 2 years after ^{131}I
10	HSD	9.9	122	2	45
11	AHH	6.1	125	7	15
12	AVS	10.6	231	2	35
13	IHD	9.0	165	7	55
14	DR	8.4	–	10	58
15	OMFC	10.5	95	15	17
16	VM	9.1	170	22	67 - needed a 2nd ^{131}I dose 2 months after 1st dose
17	MKC	7.7	128	2	12
18	CMMM	7.5	70	4.5	14
	Mean ± SD	8.0 ± 1.8	150 ± 47	8.6 ± 9.5	35 ± 17
19	EMR	12.0	260	8	51 - additional ^{131}I dose 2 months after 1st dose
20	EM	11.5	145	2.5	56
21	FRG	10.0	–	1	25
22	IBCR	10.6	130	6	33
23	MERS	7.0	130	2	36
24	OGG	5.9	119	3	18
25	HK	9.6	142	5	12
	Mean ± SD	9.5 ± 2.3	154 ± 53	3.9 ± 2.5	33 ± 16

Discussion

Toxic nodular goiter is the most prevalent cause of thyrotoxicosis in the South of Brazil

(Gross *et al.*, 1983). The most probable explanation is iodine deficiency, although the possibility of other mechanisms, such as genetic disorders (mild biosynthesis abnormalities) and goitrogenic factors (diet, pollution, etc.) cannot be excluded. Recently, thyroid growth-stimulating immunoglobulins and peptides have been associated with the development of multinodular goiter. Best known among them are the growth-promoting immunoglobulins (Drexhage, 1985).

Thyrotoxicosis in multinodular goiter develops insidiously over many years and may be precipitated by an increase in iodine ingestion (Job-Basedow phenomenon) or by the gradual increase in autonomic areas with the proportional production of thyroid hormones. Thyrotoxicosis appears when the total number of follicles with at least some degree of autonomous function has grown large enough to produce hormone in amounts exceeding the daily requirements (Gemsenjager *et al.*, 1976).

The patients in the present study were clinically in frank hyperthyroid state and had multinodular goiter on palpation of the gland. The most valuable test in the diagnosis of thyrotoxicosis was serum T4 level. Kaplan and Utiger (1978) reported that T3 toxicosis was more frequent in areas with limited iodine intake. However, the lesser discriminatory ability of serum T3 in this series could be explained by the wide range of serum T3 values in normal people from the same region (70 to 275 ng/dl), as well as by old age and associated illnesses present in our TMNG study population.

The number of patients with positive antithyroid microsomal antibodies (3/21 tested) was small and their titers were low. None had a scintigraphic pattern indicative of Graves' disease. Moreover, in a group of 43 normal individuals of approximately the same age, we found a 21% prevalence of positive antithyroid microsomal antibodies (Von Mühlen *et al.*, 1982).

Surgery has been the most indicated therapy for TMNG but its morbidity is currently regarded as excessive (DeGroot *et al.*, 1984). TMNG is generally considered to be radioresistant to ^{131}I. The large doses usually employed require hospitalization (NCRP, 1970) and sometimes can be followed by thyroid storm (Aach and Kissane, 1972). Ng Tang Fui and Maisey (1979) proposed that 15 mCi of ^{131}I could be used sucessfully in the treatment of autonomously functioning thyroid nodules. They reported that 29 out of 31 patients became euthyroid within 6 months, one patient needed a second dose and another became hypothyroid. In the present study, average time to achieve euthyroidism was 7.25 months and the number of patients with TMNG cured by the standard dose of radioactive iodine are similar to the data presented by Ng Tang Fui and Maisey. Our data thus indicate that TMNG is as sensitive to ^{131}I as goiters from non-endemic areas. Lamberg *et al.* (1959), using an average dose of 16 mCi, have found that the mean time to reach euthyroidism was 4.3 months and the frequency of hypothyroidism or treatment failure with one dose was very similar to ours. The mean follow up period (2 years and 10 months) of the patients in our study was not long enough to permit us to claim that newer cases of hypothyroidism will not occur in the future. Recently, Goldstein and Hart (1983) observed that ^{131}I therapy for autonomous thyroid adenoma caused hypothyroidism in 8 (36%) of 23 patients after a follow up period of 4 to 16.5 years (mean 8.5).

Propylthiouracil treatment did not significantly affect the therapeutic effectiveness of ^{131}I with respect to the time required to achieve euthyroidism or number of patients cured. However, the two patients who developed hypothyroidism were part of the PTU-treated group. Therefore, the role of previous treatment with an antithyroid drug in the development of hypothyroidism cannot be completely excluded. It is possible that the reduced serum thyroid hormone levels caused by the preliminary antithyroid drug therapy permitted the extranodular tissue to be stimulated by pituitary TSH and thus to concentrate ^{131}I with consequent radiation damage.

Only three patients remained thyrotoxic after the initial dose of ^{131}I, but the disease was controlled in less than 9 months after the second dose of ^{131}I. These patients did not present any particular feature that might explain this relative radioresistance.

One should also consider our observation that the same dose of ^{131}I was effective in the treatment of thyrotoxicosis irrespective of goiter size. This apparently surprising result could be explained by the fact that the goiters of the patients presented in this study probably had the same amount of functioning tissue.

Thus, the large differences in goiter size might be explained by differences in non-functioning areas. Serum thyroxine and triiodothyronine are a crude index of the amount of functioning tissue (Miller and Block, 1968), and the lack of correlation between goiter size and pretreatment T4 and T3 values observed in our patients supports this hypothesis.

A standard dose of 15 mCi ^{131}I was shown to be effective in patients from an endemic goiter region, since 80% obtained euthyroidism in a relatively short time and with a low incidence of hypothyroidism. Previous treatment with propylthiouracil does not offer advantages with respect to time to reach euthyroidism and has the major drawback of often predisposing the patient to the development of hypothyroidism.

References

Aach, R. and **Kissane, J.** (1972). Thyroid storm shortly after ^{131}I therapy of a toxic multinodular goitre. *American Journal of Medicine*, 52: 786-796.

Burke, G. (1967). The triiodothyronine suppression test. *American Journal of Medicine*, 42: 600-608.

DeGroot, L.J., Larsen, P.R., Refetoff, S. and **Stanbury, J.B.** (1984). *The Thyroid and its Diseases.* John Wiley & Sons, New York, pp. 440.

Drexhage, H.A. (1985). Immunoglobulins affecting thyroid growth. *Thyroid Today*, 8: 1-5.

Germsenjager, E., Staub, J.J., Girard, J. and **Heitz, P.H.** (1976). Preclinical hyperthyroidism in multinodular goitre. *Journal of Clinical Endocrinology and Metabolism*, 57: 915-919.

Goldstein, R. and **Hart, I.** (1983). Follow-up of solitary autonomous thyroid nodules treated with ^{131}I. *New England Journal of Medicine*, 309: 1473-1476.

Gross, J.L., Furlaneto, T.W., Kruter, R.H.E., Denardim, O.V.P., Castro, J.A.S. e **Hutz, A.** (1983). Características clínicas e laboratoriais das doenças da tireóide. *Arquivos Brasileiros de Endocrinologia e Metabologia*, 27: 89-94.

Kaplan, M.M. and **Utiger, R.D.** (1978). Diagnosis of hyperthyroidism. *Clinics in Endocrinology and Metabolism*, 7: 97-113.

Kruter, R.H.E., Liedtke, M., Castro, J.A.S. and **Gross, J.L.** (1982). T3 hyperthyroidism and thyroid cancer. *Clinical Endocrinology*, 16: 121-125.

Lamberg, B.A., Hernberg, C.A., Wahlberg, P. and **Hakkila, R.** (1959). Treatment of toxic nodular goitre with radioactive iodine. *Acta Medica Scandinavica*, 165: 245-258.

Miller, J.M. (1978). Hyperthyroidism from the thyroid follicle with autonomous function. *Clinics in Endocrinology and Metabolism*, 7: 177-197.

Miller, J.M. and **Block, M.A.** (1968). The autonomously functioning thyroid nodule. Therapeutic considerations. *Archives of Surgery*, 96: 386-392.

National Committe on Radiation Protection and Measurements (NCRP) (1970). *Precautions in the management of patients who have received therapeutic amounts of radionuclides, NCRP Report no. 37* (National Bureau of Standards Handbook 65), Washington, D.C., pp. 17-23.

Ng Tang Fui, S.C. and **Maisey, M.N.** (1979). Standard dose of ^{131}I therapy for hyperthyroidism caused by autonomously functioning thyroid nodules. *Clinical Endocrinology*, 10: 69-77.

Pendergrast, W.J., Milmore, B.K. and **Marcus, S.C.** (1961). Thyroid cancer and thyrotoxicosis in the United States: their relation to endemic goiter. *Journal of Chronic Disease*, 13: 22-38.

Sampaio, A.A. (1972). Geografia do bócio endêmico no Brasil. In: Lacaz, C.S., Baruzzi, R.G. and Siqueira, T.W. (Editors). *Introdução à Geografia Médica do Brasil*, Edgard Blucher and Editora da Universidade de São Paulo, São Paulo, pp. 476-488.

Schneider, M.A., Kruter, R.H.E., Dick, I.P., Goldim, J.R. e **Gross, J.L.** (1985). Teste do TRH. Padronização das respostas do TSH e prolactina em homens e mulheres em diferentes faixas etárias. *Arquivos Brasileiros de Endocrinologia e Metabologia*, 24: 101-105.

Studer, H., Peter, H.J. and **Gerber, H.** (1985). Toxic nodular goitre. *Clinics in Endocrinology and Metabolism*, 14: 351-372.

Von Mühlen, C.A., Eizirik, D.L., Paulam, M.A.C., Brenol, J.C.T. e **Gross, J.L.** (1982). Prevalência de tireodite auto-imune em pacientes com artrite reumatóide clássica ou definida. *Revista Brasileira de Reumatologia*, 22: 223-232.

Received September 2, 1986
Accepted October 15, 1986