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FULL PAPER

Evaluation of ^{99m}Tc-MIBI in thyroid gland imaging for the diagnosis of amiodarone-induced thyrotoxicosis

JUNQI WANG and RUIGUO ZHANG

Department of Nuclear Medicine, Tianjin First Central Hospital, Tianjin, China

Address correspondence to: Dr Junqi Wang
E-mail: *wjunqi@gmail.com*

Objective: Amiodarone-induced thyrotoxicosis (AIT) is caused by amiodarone as a side effect of cardiovascular disease treatment. Based on the differences in their pathological and physiological mechanisms, many methods have been developed so far to differentiate AIT subtypes such as colour flow Doppler sonography (CFDS) and 24-h radioiodine uptake (RAIU). However, these methods suffer from inadequate accuracy in distinguishing different types of AITs and sometimes lead to misdiagnosis and delayed treatments. Therefore, there is an unmet demand for an efficient method for accurate classification of AIT.
Methods: Technetium-99 methoxyisobutylisonitrile (^{99m}Tc-MIBI) thyroid imaging was performed on 15 patients for AIT classification, and the results were compared with other conventional methods such as CFDS, RAIU and $^{99m}TcO_4$ imaging.
Results: High uptake and retention of MIBI in thyroid tissue is characteristic in Type I AIT, while in sharp contrast, low uptake of MIBI in the thyroid tissue was observed in Type II AIT. Mixed-type AIT shows uptake value between Types I and II. MIBI imaging outperforms other methods with a lower misdiagnosis rate.
Conclusion: Among the methods evaluated, MIBI imaging enables an accurate identification of Type I, II and mixed-type AITs by showing distinct images for different types of AITs. The results obtained from our selected subjects revealed that MIBI imaging is a reliable method for diagnosis and classification of AITs and MIBI imaging has potential in the treatment of thyroid diseases.
Advances in knowledge: ^{99m}Tc-MIBI imaging is a useful method for the diagnosis of AIT. It can distinguish different types of AITs especially for mixed-type AIT, which is usually difficult to treat. ^{99m}Tc-MIBI has potential advantages over conventional methods in the efficient treatment of AIT.

INTRODUCTION

Amiodarone is commonly used as an antiarrhythmia drug and one of its side effects is amiodarone-induced thyrotoxicosis (AIT).[1–4] Owing to the wide usage of amiodarone in clinics, there is an increasing demand for the accurate diagnosis and classification of AIT for proper medical treatment.[5–7] To our best knowledge, AITs are classified into two categories conventionally based on their pathological and physiological mechanisms:[8] Type I AIT is caused by thyroid cell neoplasia and hyperthyroidism.[9] Type II AIT is characterized by the excessive release of thyroid hormone caused by degeneration of the thyroid cells.[10,11] Colour flow Doppler sonography (CFDS) and 24-h radioiodine uptake (RAIU)[12] are the two most commonly used methods for the classification of AIT in clinics. However, these two methods are usually not accurate[13] in the classification of AIT, which results in an inefficient and inappropriate treatment for AIT. Recently, technetium-99 methoxyisobutylisonitrile (^{99m}Tc-MIBI) thyroid scintigraphy has emerged as a powerful tool for quantifying thyroid-to-background ratios and differentiating AIT subtypes.[14] In addition, Piga et al[15] have compared ^{99m}Tc-MIBI thyroid scintigraphy with other imaging modalities in the diagnosis of AITs and the results showed that ^{99m}Tc-MIBI is a reliable tool for differentiating AITs. It is well known that the uptake of ^{99m}Tc-MIBI is significantly increased in neoplasia tissues,[16] while decreased in apoptosis or necrosis.[17] We envisioned that ^{99m}Tc-MIBI imaging could be a very useful tool for AIT diagnosis, which could shed light on the underlying pathological and physiological mechanisms of different AIT subtypes. The research presented herein aimed to discuss the application of ^{99m}Tc-MIBI in thyroid gland imaging for the diagnosis and classification of AIT. The efficiency and accuracy of different AIT diagnostic methods are compared and evaluated.

METHODS AND MATERIALS

Subject

15 patients (11 males, 4 females; ages from 45 to 82 years, average age 65 years) from the Division of Nuclear

Medicine in our hospital from July 2008 to December 2009 were selected. All patients were treated with amiodarone (Hangzhou Sanofi-Synthelabo Pharmaceutical Co.,Ltd., Hangzhou, China) for atrial fibrillation or atrial flutter treatment. The dosage was set as 200–400 mg per day for duration from 30 days to 3 years. The average course of treatment is 12 months. Among these patients, there are four cases of hypertension, three cases of coronary artery disease, six cases of hypertension and coronary artery disease and two cases of cardiomyopathy. None of them have any records of thyroid-related or autoimmune diseases. All of the patients have signed informed consent forms, and all experiments were approved by the ethics committee of our hospital.

Methods for the measurement of thyroid function

Free triiodothyronine, free thyroxine, thyroid-stimulating hormone, thyroglobulin antibiotics and thyroid peroxidase antibiotics were measured by Roche Cobas E601 Immunology Analyzer.

Examination of thyroid by colour flow Doppler sonography and measurement of radioiodine uptake

Ultrasound examination of the thyroid was performed on Siemens Acuson Sequoia 512 modules (Siemens Healthcare, Germany). The patients were laid on their backs with their necks exposed. Two-dimensional sonography and CFDS were carried out using a 7–12-MHz high-frequency probe. The volume of the thyroid gland, ultrasound echo pattern and thyroid nodules were recorded. The evaluation of the thyroid tissue and nodules was based on methods reported by Loy et al.[18] 3-h and 24-h RAIU were recorded by an FH 458B1 thyroid analyzer (Beijing Nuclear Medicine Equipment) after oral administration of ^{131}I- sodium iodide (150–180 kBq). 7–25% and 18–42% of the normal values verified by our hospital were set as the baselines for the 3-h and 24-h RAIU as references, respectively.

Thyroid imaging using $^{99m}TcO_4$ and technetium-99 methoxyisobutylisonitrile

Initial thyroid scan was carried out 10–15-min post-$^{99m}TcO_4$ (110–185 MBq, China Institute of Atomic Energy, Division of Isotope Research) i.v. injection. The scanning was operated with a low-energy general collimator, with energy peak of 140 kev $\pm$ 15% and 300K counts for data recording. Philips IRIX double cameral single-photon emission CT was used for imaging. The imaging results were defined as two types: positive (with clear imaging of the thyroid tissue) and negative (with no imaging of the thyroid tissue). The next day after the initial injection with $^{99m}TcO_4$, ^{99m}Tc-MIBI (185–370 MBq) (China Institute of Atomic Energy, Division of Isotope Research) was injected intravenously. Early-stage (15 min) and late-stage (60 min) scanning was carried out post-injection. The scanning was operated with a low-energy general collimator, with energy peak of 140 kev $\pm$ 15% and 300 s for data recording. The imaging results were the same as that in the initial $^{99m}TcO_4$ imaging.

Criteria for the amiodarone-induced thyrotoxicosis diagnosis and classification

Initial AIT classification: at least two of the criteria listed below must be met to be classified as Type I AIT:[13] diffuse goitre or nodular goitre; normal but uneven blood flow could be observed on CFDS image of the thyroid; RAIU value is >1%; and there is thyroid imaging when using $^{99m}TcO_4$. All the other cases which did not meet the criteria are classified as Type II AIT. Final AIT classification: the diagnosis and classification of AIT was finalized based on the efficacy to the drug treatment of the patients. Patients diagnosed with Type I AIT were treated with methimazole (MMI) (10 mg TID; Merck Co., Frankfurter, Germany), while patients diagnosed with Type II AIT were treated with prednisone (Pd) (10 mg TID; Tianjin Tianyao Pharmaceuticals, Tianjin, China). If the patients regain normal thyroid function 2–3 months after medicine treatment, we consider the diagnosis and classification of AIT accurate. Otherwise, a combined treatment with both MMI and Pd was carried out and the patients will be diagnosed of mixed-type AIT. They were monitored routinely in order to obtain the timeline for the recovery of the thyroid function.

RESULTS

Initial and final diagnosis and classification results

Image data of patients with multiple modalities (CFDS, RAIU, $^{99m}TcO^{4-}$ and MIBI imaging) were created as a comparative panorama, and the results are summarized in Table 1. 15 cases were classified and diagnosed. For initial diagnosis, 5 cases are classified as Type I and 10 cases are classified as Type II. After medicine treatment, one case which was originally classified as Type I was finally classified as mixed type, and two cases which were originally classified as Type II were finally classified as mixed type. These three mixed-type AIT cases need a combined treatment of MMI and Pd for fully recovery.

Comparison between the imaging results of thyroid using technetium-99 methoxyisobutylisonitrile

Patients diagnosed with Type I AIT all showed significantly increased uptake of MIBI and abnormal retention of MIBI (a much higher uptake than the surrounding tissues was observed and the boundary is very clear) (Figure 1a); patients diagnosed with Type II AIT did not show a high uptake of MIBI (similar uptake as compared with the surrounding tissues) (Figure 1b); and patients diagnosed with mixed-type AIT showed a slight higher MIBI uptake (slightly higher uptake than the surrounding tissues and the boundary is blurred) (Figure 1c).

Diagnosis of amiodarone-induced thyrotoxicoses using colour flow Doppler sonography, radioiodine uptake and $^{99m}TcO_4$ imaging methods

The CFDS results show that eight patients have Pattern I or II ultrasound data, which were considered as Type I AITs. When using RAIU as a guide for diagnosis of AIT, nine patients have RAIU uptake >1%, which was diagnosed as Type I AITs. When using $^{99m}TcO_4$ as the guide, only one patient (Patient 4) showed a positive image of $^{99m}TcO_4$. When RAIU method was used in combination with CFDS, three mixed-type AIT patients were not classified accurately, one patient diagnosed as Type I AIT, and two patients diagnosed as Type II AIT; however, MIBI imaging alone can accurately distinguish Type I, II and mixed-type AIT. These results are summarized in Table 2.

DISCUSSION

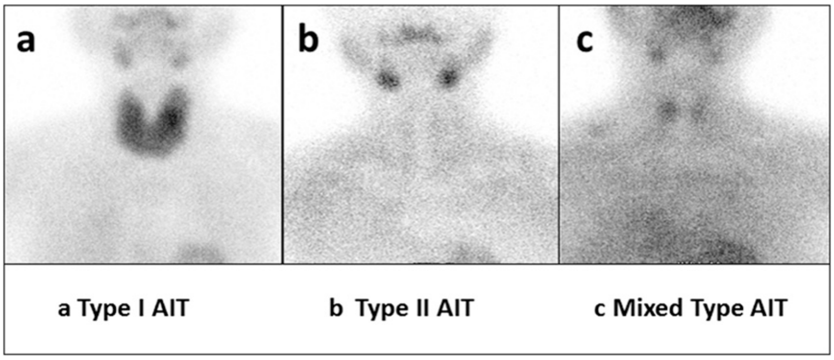
Although different types of AIT show similar symptoms, their individual mechanisms[13] are quite different and they should be

Table 1. Initial and final diagnosis of amiodarone-induced thyrotoxicoses with multiple imaging modality

Patients	Age (years)	Gender	TSH (mIU/l)	FT3 (pmol/l)	FT4 (pmol/l)	TPOAb (IU/ml)	TgAb (IU/ml)	TRAb (IU/l)	CFDS pattern	RAIU (%)	$^{99m}TcO_4^-$ imaging	MIBI imaging	Initial diagnosis	Final diagnosis
1	73	M	<0.005	25.63	91.15	115.3	200.2	5.3	PII	5.3	−	+	I	I
2	85	F	<0.005	16.28	36.85	22.4	72.5	1.5	PI	4.6	−	+	I	I
3	66	F	<0.005	25.88	62.31	28.5	115.1	0.8	PI	2.8	−	+	I	I
4	58	F	0.007	30.06	85.65	228.6	300.4	3.5	PI	9.1	+	+	I	I
5	88	F	0.007	9.39	40.75	28.7	78.9	1.3	P0	2.4	−	+?	II	I+II
6	79	F	0.012	6.87	19.52	17.3	110.6	<0.3	PI	0.5	−	+?	I	I+II
7	76	F	<0.005	9.46	30.26	105.4	64.5	0.9	PI	0.2	−	+?	II	I+II
8	91	M	0.009	10.41	30.06	17.8	89.2	<0.3	P0	1.4	−	−	II	II
9	55	M	0.007	7.63	23.76	29.5	74.0	<0.3	P0	1.6	−	−	II	II
10	71	M	<0.005	12.10	70.78	19.7	99.7	0.6	PI	0.2	−	−	II	II
11	48	M	0.006	16.11	53.09	17.4	225.3	<0.3	P0	1.3	−	−	II	II
12	76	M	<0.005	9.54	35.79	24.6	78.5	<0.3	PI	0.1	−	−	II	II
13	69	F	<0.005	8.72	25.32	78.5	102.8	0.7	P0	0.7	−	−	II	II
14	77	M	0.017	7.44	31.67	27.2	44.7	<0.3	P0	1.4	−	−	II	II
15	58	M	0.008	8.08	36.12	17.3	72.3	<0.3	P0	0.3	−	−	II	II

^{99}Tc, technetium-99; CFDS, colour flow Doppler sonography; F, female; FT3, free triiodothyronine; FT4, free thyroxine; M, male; MIBI, methoxyisobutylisonitrile; RAIU, radioiodine uptake; TgAb, thyroglobulin antibiotics; TPOAb, thyroid peroxidase antibiotics; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone.
Normal value: TSH (0.27–4.2), FT3 (3.1–6.8), FT4 (12.0–22.0), TPOAb (0.00–34.00), TgAb (0–115) and TRAb (0–1.75).
− is negative, + is positive, +? is suspicious positive.
CFDS patterns: (1) Pattern 0 (P0) comprises the absence of intraparenchymal vascularity or minimal spots; (2) Pattern I (PI) comprises the presence of parenchymal blood flow with patchy uneven distribution; (3) Pattern II (PII) comprises mild increases in power Doppler signals with patchy distribution; and (4) Pattern III (PIII) comprises significant increases in power Doppler signals with diffuse homogeneous distribution.

Figure 1. Technetium-99 methoxyisobutylisonitrile imaging of the thyroid for different types of amiodarone-induced thyrotoxicoses (AITs). (a) diffused obvious uptake of MIBI by thyroid tissue-clear imaging of the thyroid tissue, (b) no uptake of MIBI by thyroid tissue-no imaging of the thyroid tissue, (c) heterogeneous decrease uptake of MIBI by thyroid tissue.



treated differently. The difficulty of the diagnosis of AIT is not the identification of the status of thyrotoxicosis, but rather the identification of its pathological and physiological mechanisms. Simple classification of AIT into Types I and II is not sufficient in distinguishing all kinds of AIT types, since there are also types where the growth and degeneration of thyroid cells coexist.[19] A lot of the inefficient medical treatments are caused by misdiagnosis of AITs. As illustrated in Table 1, CFDS method misdiagnosed five patients (Patients 5, 6, 7, 10 and 12). All Type I cases have detectable RAIU, but four cases (Patients 8, 9, 11 and 14) of Type II AIT and one case (Patient 5) of mixed-type AIT also showed detectable RAIU. Therefore, five cases in total were misdiagnosed using RAIU. Only one case (Patient 4) of Type I AIT was successfully diagnosed imaged by $^{99m}TcO_4$ imaging, and the rest of the cases were misdiagnosed as Type II AIT, while the results obtained from MIBI imaging data perfectly match the final diagnosis results.

This study has shown that MIBI imaging could be used as an efficient tool for AIT diagnosis and classification. Hyperthyroidism tissues usually show high level of cell proliferation and metabolism, which in turn results in high uptake and retention of MIBI.[20] Since Type I AIT is caused by thyroid cell neoplasia and hyperthyroidism, it should give rise to a high uptake of MIBI. On the other hand, Type II AIT is caused by degeneration of thyroid cells. Therefore, there is no significant uptake of MIBI.[21] Subacute thyroiditis is a very common cell degenerative thyrotoxicosis, but unlike Type II AIT where only minor lymphocytic and plasma cell infiltration was observed,[21] there will be formation of granuloma during the acute phase of subacute thyroiditis. And the formation of granuloma is often indicated by high uptake of MIBI. Patients with mixed-type AIT show slight uptake of MIBI, possibly owing to the trade-off between an uncompleted degeneration of thyroid and different extent of hyperthyroidism.[19]

In our study, MIBI imaging has shown higher value in AIT diagnosis and classification than conventional methods. Firstly, MIBI imaging is more accurate than TcO_4 imaging, and there was only one positive result for Type I AIT out of all four patients with Type I AIT. This result further indicates the disadvantage of $^{99m}TcO_4$ in AIT diagnosis and classification.[22] Although CFDS and RAIU is considered to be the optimal method for AIT diagnosis, Tanda et al[19]reported that 15–17% cases are still misdiagnosed using CFDS and RAIU. In line with previous reports,[18] our study also shows that the combination of CFDS and RAIU is indeed very efficient in distinguishing Type I and II AITs. However, some patients with Type II and mixed-type AITs were misdiagnosed as Type I AIT by using CFDS and RAIU. Our results showed that it is reasonable to believe that MIBI imaging has advantage in AIT diagnosis and classification.

In summary, ^{99m}Tc-MIBI imaging is a very valuable method for the diagnosis and classification of AIT. It can distinguish different types of AITs especially for mixed-type AIT, which is usually difficult to cure. ^{99m}Tc-MIBI has shown great advantages over conventional methods in the efficient treatment of AIT.

Table 2. Diagnosis and classification of amiodarone-induced thyrotoxicosis using different methods

Final classification	Diagnostic methods				
	CFDS	RAIU	$^{99m}TcO_4$	CFDS + RAIU	MIBI
Type I	8	9	1	5	4
Type II	7	6	14	10	8
Mixed type	0	0	0	0	3

^{99}Tc, technetium-99; CFDS, colour flow Doppler sonography; RAIU, radioiodine uptake MIBI, methoxyisobutylisonitrile.

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