SHORT COMMUNICATION

Risk of iodine-induced thyrotoxicosis after coronary angiography: an investigation in 788 unselected subjects

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Abstract

In this study, the risk of iodine-induced thyrotoxicosis in unselected patients from an iodine-deficient area was investigated. The patients were consecutively enrolled. Thyroid hormone values and urinary iodine excretion were determined before, as well as 1, 4 and 12 weeks after iodine contamination by coronary angiography. Two of 788 unselected patients developed hyperthyroidism within 12 weeks. The two patients did not belong to a risk group for iodine-induced thyrotoxicosis (i.e. old people, patients with goiter or possible thyroid autonomy, low TSH). Both patients had normal TSH levels at baseline and ultrasound of the thyroid was without evidence of nodules. The study shows that in euthyroid unselected patients from an iodine-deficient area short-term iodine contamination by contrast media rarely leads to hyperthyroidism. On account of these facts, prophylactic therapy, e.g. by perchlorate or thiamazole, is not generally recommended, because the risk of side-effects is perhaps even greater than the risk of iodine-induced thyrotoxicosis.

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Introduction

There are many causes for the development of thyrotoxicosis. Two main reasons are Graves' disease caused by autoimmunity and hyperthyroidism on the basis of thyroid autonomy. Iodine-induced thyrotoxicosis (IIT) belongs to the second group. As early as 1820 the correlation of clinical symptoms of hyperthyroidism and iodine contamination in subjects with goiter had been described (1). At the beginning of this century, Breuer (2) and Kocher (3) made further investigations concerning these facts. Today it is an accepted theory that in subjects with pre-existing thyroid autonomy, iodine contamination can result in IIT. Iodine deficiency is an important factor for the development of autonomy and goiter (4, 5), and with the size of the goiter the probability of autonomy rises (6). Therefore, IIT is more common in areas with low iodine intake such as Germany (7). IIT can also occur in areas with sufficient iodine intake (8) but patients from an iodine-deficient area are even more endangered, as recently reviewed by Stanbury *et al.* (9). In contrast, correction of mild iodine deficiency leads to a decrease in the incidence of toxic nodular goiter (10).

The inadvertent administration of iodine happens through various substances: iodine-containing drugs, disinfectants, antiseptics and even contrast agents. A

widely used iodine-containing drug is amiodarone, which contains 75 mg iodine per 200 mg tablet. The drug has been responsible for numerous instances of IIT (11, 12). Another major source of iodine is iodized oil, sometimes given as goiter treatment (13). IIT has been described even in apparently normal thyroid glands (14). On account of these facts it is quite usual (for example in cardiology departments) to examine the thyroid gland and take blood samples for thyroid hormone measurement before patients undergo coronary angiography. Furthermore, many physicians recommend a preventive treatment with antithyroid drugs, although there are no data about the individual risk of IIT after contrast media contamination. Sufficient studies on the advantage of such prophylactic therapy are not available.

The following investigation was performed to determine the individual risk for the development of iodine-induced thyrotoxicosis in subjects from an iodine-deficient area. From the results of this study the question of the value of prophylactic therapy will be answered.

Subjects and methods

Seven hundred and eighty-eight (788) patients who underwent elective coronary angiography in Roderbirken (Leichlingen, Germany) were admitted to this study. Except for taking iodine-containing drugs or known

hyperthyroidism there were no criteria for exclusion; particularly there was no age limit. During clinical examination, history was taken and an ultrasound of the thyroid was performed. Nodules, cysts and the volume of the thyroid were recorded. An enlarged thyroid gland was defined as a volume exceeding 18 ml in females and 25 ml in males (15). Basal thyrotrophin (TSH), free thyroxine (FT₄), thyroid antibodies against thyroid peroxidase (TPO) and urinary iodine were measured at four different time points: before coronary angiography (point I), 7 days after (point II), 4 weeks after (point III) and 12 weeks after coronary angiography (point IV). The blood samples at time points II–IV were taken by the family practitioner and sent by post.

Overt hyperthyroidism was defined on the basis of the finding of elevated FT₄ and suppressed TSH in combination with clinical signs. Subclinical hyperthyroidism was diagnosed on the basis of suppressed TSH and normal FT₄ values. Overt hypothyroidism was defined on the basis of the finding of elevated TSH with lowered FT₄. Subclinical hypothyroidism was diagnosed when TSH was elevated and FT₄ normal.

TSH and FT₄ were assayed with a commercial kit (ES 600, Boehringer Mannheim GmbH, Mannheim, Germany); normal ranges were 0.25–3.1 µU/ml for basal TSH and 10.3–25.8 pmol/l for FT₄. Thyroid antibodies were measured with a Cent AK Anti-TPO kit (Medipan Diagnostics GmbH, Selchow, Germany; normal range <40 U/l). Urinary iodine was determined by the cersulfate method described elsewhere (16). Before coronary angiography, urinary iodine excretion was measured in all subjects, later only if all four urine samples had been collected.

Coronary angiography itself was carried out with different amounts of UltravistR (370 mg iodine/ml; Schering AG, Berlin, Germany).

Statistical comparisons were made by the Wilcoxon test, always related to the data of point I. Data for TSH, FT₄ and urinary iodine are given as median values. The study design was approved by the Ethical committee of the Heinrich-Heine University, Duesseldorf.

Results

The mean age of the 788 patients (659 male, 129 female) was 55 ± 7.4 years ($x \pm s.d.$, range 27–84 years). Figure 1 shows the age distribution of the whole group. The mean thyroid volume in 788 subjects was 18.3 ml (range 2.6–77.6 ml). In 133 cases (16.9%) nodules and in 35 cases (4.4%) cysts were seen. In 109 males (16.5%) thyroid volume exceeded 25 ml, and in 35 females 18 ml (27.1%) (15). Positive thyroid history was recorded in 103 patients (13.7%).

Hyperthyroidism

At the beginning of the study, serum TSH levels were lower or completely suppressed with FT₄ in the normal

Figure 1 Age distribution of the 788 subjects studied.

range ('subclinical hyperthyroidism') in 27 of 710 subjects (3.8%). One week later this constellation was found in 15 of 572 patients (2.6%), after 4 weeks in 27 of 547 subjects (4.9%) and at the end of the study in 19 of 464 patients (4.1%). Only two subjects had newly developed subclinical hyperthyroidism at time point II. In the remaining patients, subclinical hyperthyroidism already existed at baseline.

In three cases, hyperthyroidism (suppressed TSH, elevated FT₄) was recorded.

One of these three patients showed hyperthyroidism before undergoing coronary angiography (TSH 0 µU/l, FT₄ 52.3 pmol/l). Because of the urgent indication the examination was performed. One week after coronary angiography slight hyperthyroidism was still documented while taking thiamazole (TSH 0.02 µU/l, FT₄ 31.2 pmol/l), whereas 12 weeks after receiving contrast media euthyroidism under therapy was documented (TSH 1.76 µU/l, FT₄ 17.9 pmol/l). No blood sample was taken at time point III. Hyperthyroidism in this case was not connected with the application of contrast medium and was obviously not caused by the angiography.

In two other subjects thyrotoxicosis was first diagnosed 4 weeks after coronary angiography.

At this time point, TSH of the first patient was suppressed to 0.05 µU/l and FT₄ elevated to 69.4 pmol/l. Ultrasound and palpation of the thyroid were normal; thyroid volume was 22.6 ml. This 68-year-old man took no drugs affecting the thyroid, thyroid history was negative, and he had never received contrast media before. Anti-TPO antibodies were positive ranging from 506 to 2399 U/l at time point II–IV; TSH was 1.34 µU/ml and FT₄ 17.0 pmol/l at point II, and at the end of the study TSH was 0.08 µU/ml and FT₄ 69.5 pmol/l. The blood sample before coronary angiography showed normal values for FT₄ and TSH.

The second patient was a 55-year-old male. Sonography and examination of the thyroid did not show nodules or cysts. The volume of the thyroid was 18.5 ml with a normal echographic pattern. History was negative, the patient took no drugs affecting the thyroid and had never received contrast agents before. Anti-TPO antibodies

were always below 40 U/l at all four time points. Before and 1 week after the iodine exposure euthyroidism was found (TSH 0.67 μ U/ml, FT₄ 17.9 pmol/l and TSH 0.68 μ U/ml, FT₄ 22.6 pmol/l). At time point III TSH was 0.02 μ U/ml and FT₄ was 59.3 pmol/l. The family practitioners of all three patients were informed, and all patients received antithyroid therapy.

Hypothyroidism

Overall ten cases of overt hypothyroidism with elevated TSH and low FT₄ levels were detected in the study. In two subjects hypothyroidism at time point I returned to normal at the end of the study. Six cases of hypothyroidism were first seen 1 week after coronary angiography; half of them showed an elevated TSH at time point I with normal FT₄. In four of these six subjects normalization took place at point III, in the other two cases no blood sample was taken at point IV. Two patients developed hypothyroidism 12 weeks after undergoing coronary angiography. At time points before, they showed elevated TSH with FT₄ in the normal range.

Table 1 summarizes the prevalence of thyroid dysfunction observed in the study. Subclinical hypothyroidism was defined as an elevation of TSH with normal FT₄ values.

TSH, FT₄ and urinary iodine concentrations

All values listed below are given as median values. At the beginning of the study, a mean TSH level of 1.25 μ U/ml (range 0–37.22 μ U/ml) was found in 717 subjects. One week later TSH significantly ($P < 0.0001$) increased to 1.69 μ U/ml (range 0.02–26.17 μ U/ml) in 575 subjects. Four weeks after coronary angiography, TSH decreased significantly ($P = 0.0006$) to 1.12 μ U/ml (range 0–8.43 μ U/ml, $n = 493$), and at the end of the study the TSH level in 417 subjects was 1.26 μ U/ml (range 0–6.17 μ U/ml, $P = \text{NS}$ vs basal).

At the beginning of the study, the median value of FT₄ in 729 subjects was 16.6 pmol/l (range 7.2–90.3 pmol/l). FT₄ declined 7 days after coronary angiography to 16.0 pmol/l (range 1.3–73.7 pmol/l, $n = 622$), after 4

weeks to 16.1 pmol/l (range 8.1–69.4 pmol/l, $n = 552$) and after 12 weeks to 15.5 pmol/l (range 1.2–69.5 pmol/l, $n = 471$). The decrease of FT₄ from the base value (point I) to the other time points was always significant (to point II and IV $P < 0.0001$ and to point III $P = 0.0002$).

Before undergoing coronary angiography, urinary iodine (median) in 671 patients was 34 μ g/g creatinine with a maximum of 25 330 μ g/g creatinine and a minimum of 0 μ g/g creatinine. One week after receiving contrast dyes, urinary iodine in 367 subjects increased to 1109 μ g/g creatinine. Four weeks after coronary angiography a median value of 57 μ g/g creatinine in 367 patients, and after 12 weeks a value of 49 μ g/g creatinine in 367 subjects was found. The increase at time point II–IV was always significant ($P < 0.0001$) compared with basal values.

Discussion

There is no doubt that iodine-containing drugs can cause hyperthyroidism. Most of the cases of IIT occur in subjects with thyroid autonomy. There are many studies describing IIT through different iodine-containing drugs, but there are no studies about the risk of iodine-induced hyperthyroidism in unselected patients from an iodine-deficient area. The main aim of this study therefore was to quantify the risk of iodine-induced hyperthyroidism. Only three of 788 patients showed hyperthyroidism, and only two cases can be connected to the iodine exposure through coronary angiography. Remarkably, the pre-existing hyperthyroidism before coronary angiography in one patient was not aggravated by iodine exposure; thiamazole treatment resulted in normalization of hormone values and no increase after angiography was documented. Two patients developed iodine-induced hyperthyroidism. The low risk ($< 0.3\%$) for developing IIT represents the main result of this study.

Patients showing iodine-induced hyperthyroidism in this study do not belong to the so-called risk group (9, 17). In both cases the thyroid gland volume was within the normal range, TSH was not suppressed before and 7 days after coronary angiography and

Table 1 Prevalence of thyroid dysfunction among patients studied (percentage of patients available at different time points).

Time point*	Patients with subclinical hyperthyroidism	Patients with overt hyperthyroidism	Patients with subclinical hypothyroidism	Patients with overt hypothyroidism
I	3.8	0.1	4.2	0.3
II	2.6	0.2	14.3	1.4
III	4.9	0.4	4.0	0.6
IV	4.1	0.2	3.6	0.4

*Time points: I: before coronary angiography; II: 7 days after coronary angiography; III: 4 weeks after coronary angiography; IV: 12 weeks after coronary angiography.

neither patient was very old. According to the literature, the risk group for the development of IIT can be described as patients of old age, patients with an enlarged thyroid gland and especially with multinodular goiter, and patients with a possible autonomy (low TSH) (6). At the start of this study, 3.8% of all patients showed low TSH levels, and a thyroid enlargement in 23.3% was noticed, but no patient of the risk group developed hyperthyroidism. The two cases of iodine-induced thyrotoxicosis in our study occurred in subjects with an apparently normal gland. According to these facts it cannot be established which patients should be selected to receive a prophylactic therapy. In one study the effect of prophylactic therapy on the development of iodine-induced hyperthyroidism has been examined; Nolte *et al.* (18) investigated 51 patients undergoing coronary angiography. They received 20 mg thiamazole or 900 mg sodium perchlorate before and after coronary angiography or received no therapy. Overall, four subjects developed hyperthyroidism, two in the untreated group and one each in the treated groups. Patients having a risk of hyperthyroidism are not recognizable with certainty by sonography of the thyroid gland or blood samples. Based on our observations, we do not support preventive measures as recommended by others (18). The study of Nolte *et al.* (18) even shows that iodine-induced hyperthyroidism cannot be prevented by prophylactic therapy in every case. At this point it should be mentioned that the risk for side-effects of carbimazole (leukopenia 0.4%, thrombocytopenia 0.2%, agranulocytosis 0.2%) (19) is even higher than the risk of iodine-induced hyperthyroidism. Experimental therapy can only be recommended when there is a high level of justification. This justification seems not to exist in the question under study, because of the low risk, and because it is not clear which selected subjects should receive prophylactic therapy. As early as 1980, Skare & Frey (20), as well as others earlier (14), reported iodine-induced hyperthyroidism in apparently normal glands. Our data agree with the results of these studies. Therefore we also do not support the demand for thyroid scintigraphy in subjects with nodular goiter before they receive contrast dyes. Further studies are needed to show whether the results of our observation also apply to other ways of iodine exposure. Additionally, from our data no information on the risk of hyperthyroidism in cases of long-term iodine contamination (e.g. iodine tablets or amiodarone) can be deduced.

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