Prophylactic application of thyrostatic drugs during excessive iodine exposure in euthyroid patients with thyroid autonomy: a randomized study

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In a prospective, randomized study we examined the influence of prophylactic short-term thyrostatic therapy on thyroid iodine metabolism in patients with euthyroid autonomy undergoing elective coronary angiography. From a total of 1177 patients, 51 fulfilled the criteria of euthyroid autonomy before coronary angiography (negative thyrotropin-releasing hormone test, 10-min uptake of at least 1.2% 99mTc and no elevation of free thyroxine and free triiodothyronine indices) and were randomized into three groups: group 1 (N = 17) received 20 mg/day of thiamazole and group 2 (N = 17) received 900 mg/day of sodium perchlorate; thyrostatic therapy was begun on the day before angiography and continued for 14 days; group 3 (N = 17) served as controls without treatment. Parameters of thyroid function—free thyroxine (FT4) index and free triiodothyronine (FT3) index, thyrotropin (TSH) and delta-TSH—urine iodine excretion and 99mTc uptake were determined before and 30 days after coronary angiography. At the end of the study the mean FT4 index and FT3 index were elevated significantly in the control group compared with baseline values, but were still within the normal range. In contrast, the mean FT4 index and FT3 index remained unchanged in the treated groups. Four mild cases of hyperthyroidism were observed at the end of the study: two cases in the control group and one case in each of the treated groups. Thyrotropin suppression, urine iodine excretion and 99mTc uptake differed significantly between the treated groups and the control group. In the treated groups TSH suppression, urine iodine excretion and 99mTc uptake remained unchanged 30 days after coronary angiography compared with baseline values. In the control group the degree of TSH suppression and the level of urine iodine excretion increased (about twofold) significantly after coronary angiography, whereas 99mTc uptake decreased significantly (ca. 50%). In conclusion, short-term prophylactic thyrostatic therapy seems to have a protective effect against iodine excess in patients with euthyroid autonomy. However, mild hyperthyroidism could not be prevented in some cases. Probably a combination therapy of thiamazole and perchlorate would be more effective.

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Nearly 15% of all cases of thyrotoxicosis in western Europe countries are characterized by iodine contamination (1, 2). Iodine contamination can even lead to thyrotoxic crisis (3). Hyperthyroidism due to an iodine overload occurs more often in iodine-deficient areas like Germany than in regions with sufficient iodine supplementation (4). The reason for this finding is generally seen in an increased prevalence of goitres with functional autonomy (1, 5–7). Particularly in high-risk patients (goitrous growth with autonomy and TSH suppression), iodine-containing drugs may lead to hyperthyroidism or aggravate a hyperthyroid state (4, 8–13). As drug therapy of iodine-induced hyperthyroidism may be difficult (14, 15) and sometimes not effective, a preventive (prophylactic) application of thyrostatic drugs has been proposed in high-risk patients if the application of iodine-containing drugs, especially contrast dyes, is necessary (16). The effectiveness of a prophylactic thyrostatic treatment has been suggested by animal experiments in nude mice transplanted with autonomous adenoma tissue (17). To our knowledge, there is not a prospectively controlled and randomized study in humans that investigates the effect of a prophylactic application of thyrostatic drugs during excessive iodine exposure in patients with euthyroid autonomy. We therefore initiated a prospectively controlled and randomized pilot study in patients with euthyroid functional autonomy to compare the effectiveness of the prophylactic short-term administration of thiamazole and sodium perchlorate in preventing changes of thyroid function and iodine metabolism after application of iodine-containing contrast media during elective coronary angiography (CA).
Subjects and methods

Subjects

Patients from all regions of Lower Saxonia (northern Germany; an area of moderate iodine deficiency) who were admitted to our hospital for elective CA from May 1992 up to December 1994 were screened for TSH. If TSH levels were reduced (<0.4 µU/ml), thyroid parameters (FT4 index and FT3 index) were determined and a TRH test and thyroid scintigraphy were performed. Inclusion criteria were: normal FT3 index and normal FT4 index, delta-TSH <3.5 µU/ml and a 99mTc uptake (TcU) of more than 1.1% (in order to exclude patients with concurrent iodine contamination for other reasons). Exclusion criteria were: manifest hyperthyroidism, large autonomous adenoma, immunogenic thyroid disease, urine iodine excretion of more than 200 µmol/mol creatinine, instable angina pectoris, second disease with a Karnofsky index of less than 50%, patients older than 75 years or younger than 40 years, application of contrast media in the last 6 months and the concomitant use of thyroid hormones, thyrotoxic drugs or amiodarone.

The study was approved by the local committee on medical ethics, and written informed consent was obtained from the patients.

A total of 1177 hospitalized patients consecutively undergoing elective CA were screened, 1126 patients had to be excluded mainly because of normal TSH (1044 subjects), organzatory problems (34 subjects), 99mTcU < 1.2% (17 subjects), pre-existing hyperthyroidism (15 subjects) and a Karnofsky index <50% (16). Only a minority of 51 patients fulfilled the inclusion criteria and took part in the study.

Protocol

Patients fulfilling the criteria described above were randomly assigned to one of the following three therapeutic regimens:

- **group 1** received 20 mg of thiamazole once a day;
- **group 2** was treated with 900 mg of sodium perchlorate (300 mg three times a day);
- **group 3** represented the control group and received no special therapy.

Each group contained 17 patients. Treatment was begun 1 day before angiography and lasted for 14 days. Baseline parameters included thyroid values (T3U, T4, FT4 index, T3, FT3 index, TSH and delta-TSH), determination of urine iodine excretion, thyroid scintigraphy and sonographic thyroid volumetry. Thyroid parameters were controlled 30 days after CA. An ambulatory control was done with determination of the following parameters: thyroid values (T3U, T4, FT4 index, FT3 index, TSH, delta-TSH at baseline (0 days) and 30 days after coronary angiography.

| Table 1. Mean values ± so of free T4 index (FT4), FT3, TSH and delta-TSH at baseline (0 days) and 30 days after coronary angiography. |
|--------------------|-------|-------|---|
| FT4 (µU/ml) | 0 days | 30 days | P |
| Thiamazole                  | 7.5 (1.2) | 7.4 (1.2) |       |
| (group 1)                  |       |       |       |
| Perchlorate                 | 7.8 (1.7) | 7.4 (1.7) |       |
| (group 2)                  |       |       |       |
| Control                    | 7.4 (1.3) | 8.5 (2.0) | 0.026 |
| (group 3)                  |       |       |       |
| FT3                       | 132 (22) | 134 (25) |       |
| Thiamazole                  |       |       |       |
| (group 1)                  |       |       |       |
| Perchlorate                 | 129 (20) | 133 (24) |       |
| (group 2)                  |       |       |       |
| Control                    | 131 (13) | 150 (25) | 0.013 |
| (group 3)                  |       |       |       |

- FT4 index, T3, FT3 index, TSH, delta-TSH, urine iodine excretion and thyroid scintigraphy.

Methods

Total T4 (T4), free T4 index (FT4I), total T1 (T1), free T3 index (FT3I), T3 uptake (T3U), TSH and TSH response (delta-TSH) 30 min after 200 µg of TRH iv were determined using commercially available kits, including an ultrasensitive assay for TSH measurement. Total iodine excretion in the urine was measured by a Technicon autoanalyser (18). Five minutes after iv injection of 37 MBq (1 mCi) of 99mTc sodium pertechnetate, thyroid scintigraphy was performed with a preset time of 10 min and total 99mTc uptake (TcU) of the thyroid gland was determined (19). Thyroid volume was measured by real-time ultrasound (Comisons 310 A, Kretz, Wiesbaden) (20). Normal values were ≤ 18 ml for women and ≤ 25 ml for men.

As a contrast medium we used Urografin 76% (0.1 g/ml diatrizoate sodium, 0.66 g/ml diatrizoate meglumine and 0.37 g/ml iodine, Schering, Berlin).

Statistical analysis

Comparative results of repeated measurements were analysed by two-tailed Student’s t-test for paired
samples, with a significant level of \( p = 0.05 \). Data were expressed as means \( \pm \) sd.

Results

Fifty-one patients (35 males and 16 females) took part in the study. The mean age was 63 years and ranged from 46 to 75 years. The mean volume of contrast medium was 149 ml and ranged from 50 to 410 ml. Thyroid volume was increased on average (mean 54.4 ml, range 16.3–180 ml): 25% of patients showed nodulous goitres, 67% had diffuse goitres and 8% showed a normal thyroid gland. There was no significant difference between groups 1, 2 and 3 with regard to age, sex, mean volume of contrast media and goitre size. Side effects of thyrostatic drugs were not observed.

Mean FT\(_4\) and FT\(_3\) were elevated significantly in the control patients 30 days after CA compared with baseline values, but were still within the normal range. In contrast, the mean FT\(_4\) and FT\(_3\) remained unchanged in the treated groups (Table 1). The corresponding TSH and delta-TSH values were suppressed before CA in all patients and remained suppressed after CA in most of the patients. Furthermore, mean TSH and mean delta-TSH still decreased significantly in the control group 30 days after CA in comparison with the baseline values (ca. 50% reduction in TSH and delta-TSH: Table 1). In the treated groups, the mean TSH and mean delta-TSH remain unchanged or even significantly increased (mean TSH after 30 days in the thiamazole group). Hyperthyroidism (suppressed TSH and increased FT\(_4\) and/or FT\(_3\)) was observed in four patients. The FT\(_4\) and/or FT\(_3\) were only slightly elevated (in two patients of the control group and in one patient in each of the treated groups). Clinical symptoms could be found only in two of the patients (one in the sodium perchlorate and one in the control group). The corresponding values for risk factors like goitre size, age, volume of contrast dye, basal TSH, TcU and urine iodine excretion showed heterogeneous alterations and did not differ between the group that developed hyperthyroidism and the one that did not. No single risk factor could be found, that was consistently changed in one direction in all four patients and could predict hyperthyroidism. Treatment with thyrostatic drugs was not necessary in any case.

Overt hypothyroidism (defined as increased TSH and reduced FT\(_4\)) was not observed in any patient.

The TcU was \( \geq 1.2\% \) in all patients before CA. Thirty days after CA, TcU showed both decreases as well as increases in all groups. On average, the alterations of TcU were minimal in both of the treated groups (Table 2). In contrast, the mean TcU was changed significantly in the control group with a reduction of nearly 50% 30 days after CA, indicating persistent iodine contamination of the thyroid.

Iodine excretion was within the reference range before CA in most of the patients in all groups and never reached the upper limit of 200 \( \mu \)mol/mol creatinine above which iodine contamination of the thyroid is assumed. Mean iodine excretion was normal in all groups before CA (Table 2). Thirty days after CA, mean iodine excretion remained normal in both of the treated groups but was increased significantly (about twofold) in the control group.

Discussion

The present study shows that in patients with euthyroid functional autonomy and increased risk for the development of iodine-induced hyperthyroidism, thiamazole and sodium perchlorate have some protective effect during iodine contamination when given prophylactically. Thirty days after CA the following effects of prophylactic short-term treatment were seen. Firstly, iodine excretion did not change in the treated groups but increased significantly in the controls, suggesting a more efficient iodine elimination in the treated groups. Secondly, TcU was virtually unchanged compared to uptake before iodine contamination in the treated groups, indicating that the intrathyroidal free iodine store was not increased. In the control group the uptake was still significantly suppressed at this time, indicating an increased intrathyroidal free iodine store. Thirdly, a decrease of TSH and delta-TSH 30 days after CA in the control group (halving of TSH and delta-TSH) reflected an increased hormone production in the untreated patients. In contrast, the TSH level remained unchanged or even increased in the treated patients. Consequently, the mean FT\(_4\) and FT\(_3\) were elevated significantly in the control groups compared with baseline values whereas the mean FT\(_4\) and FT\(_3\)
remained unchanged in the treated groups, indicating that both drugs were effective in preventing iodine-induced changes in a group of patients with partial autonomy.

Despite these significant effects, one patient with a small and short-term elevation of thyroid hormones was observed in each of the treated groups. This implies that both drugs at the applied doses were not able to totally prevent thyrotoxicosis.

The incidence of mild hyperthyroidism in the whole group (four from 51 patients, 7.8%) seems to be higher in our selected patients than in the group of unselected patients of Hintze et al. (21), (two from 710 patients, 0.3%). A clinical study using a prophylactic treatment with methimazole and perchlorate in unselected euthyroid patients (N = 60) from an area of moderate iodine deficiency, who underwent CA, showed no case of hyperthyroidism in the control group or in the treated group (22). The definition of a risk group for patients with euthyroid autonomy, therefore, seems to be justified.

When considering a prophylactic thyrostatic therapy it is important to define risk factors for the development of iodine-induced hyperthyroidism. The risk of iodine-induced hyperthyroidism depends on the individual risk of a patient as well as on the iodine load (4). However, none of the different risk factors (goitre size, age, volume of contrast media, degree of TSH suppression, TCU and urine iodine excretion) could predict the few patients who finally developed hyperthyroidism. From the literature, a suppression uptake of >2% seems at present the best-established parameter to define a high degree of autonomy and an increased risk of iodine-induced thyrotoxicosis (23). However, suppression uptake in most cases is not available in the acute clinical situation.

One potential risk factor even in a non-iodine-deficient area seems to be age. Recently it was shown that even in an area with sufficient iodine supply, elderly people (older than 70 years) had an increased risk of iodine-induced hyperthyroidism (24), probably as a consequence of an increased prevalence of autonomy in patients older than 70 years.

Discussing the use of a prophylactic thyrostatic therapy, the potential side effects of thyrostatic drugs must be regarded (25). In our study, side effects of thyrostatic therapy were not observed, but larger studies will be needed to clarify this point.

Finally, in respect to the clinical relevance of the results presented, we would like to draw the following conclusion: prophylactic application of thiamazole and perchlorate favours the elimination of excess iodine in risk patients with functional autonomy. However, because the pathophysiological reason for fulminating thyrotoxicosis in some rare patients is unclear, we cannot exclude that a prophylactic treatment of the kind performed here would reduce the occurrence of mild thyrotoxicosis but would not alter the clinical course of severe cases. Short-term thyrostatic therapy seems to be well tolerated. As hyperthyroidism could not be prevented totally by monotherapy with either thionamide or perchlorate, a combination therapy with thionamide and sodium perchlorate in risk patients could be more effective and should be tested in further trials.

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References


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