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A low incidence of iodine-induced hyperthyroidism following administration of iodinated contrast in an iodine deficient region

Short title: Low incidence of hyperthyroidism following iodinated contrast.

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Abstract

Objective: There is limited data on the incidence of iodinated contrast induced thyrotoxicosis, particularly in iodine deficient regions. The aim of this study was to determine the incidence of iodinated contrast-induced thyrotoxicosis and to determine whether thyrotoxicosis was more common in patients ≥70 years compared to those <70 years of age.

Design: A prospective study of adult patients undergoing an outpatient CT with iodinated contrast was performed.

Measurements: Thyroid function tests (TFTs) and urine iodine measurements were performed prior to the scan. TFTs were repeated at 4- and 8-weeks post scan. Changes in TFTs from baseline were analysed.

Results: A total of 102 patients were included in the final analysis. Overall, TSH levels dropped (p=0.01), and free T_3 (FT_3) levels increased (p=0.04) between baseline and week 4 with normalisation by week 8, however these changes were not considered clinically significant. No significant differences in free T_4 (FT_4) occurred in the overall group (p=0.82). There were no differences in TFTs between baseline and 4- or 8- weeks for those patients aged <70 compared to ≥70 years. Two patients developed new subnormal TSH values. Of these, one had a 90mm follicular variant papillary thyroid carcinoma diagnosed while the other had a normal thyroid assessment and TSH spontaneously normalised by 12 weeks.

Conclusions: Only 2% of patients developed subclinical hyperthyroidism following a standard dose of iodinated contrast for CT investigations. Given the low incidence of iodine-induced thyrotoxicosis, there is no indication for routine pre- and post-CT thyroid function testing in our region.

Introduction

Due to increasing use of contrast-enhanced computed tomography (CT) and angiography, patients are frequently exposed to large amounts of iodinated contrast. The current recommended daily intake of iodine for non-pregnant, non-lactating adults is 150 mcg per day.[1] This compares to the amount found in iodinated contrast media (ICM), which ranges from 270-350 mg iodine/mL. The typical exposure from a CT scan is 35,000 mg iodine, which results in an acute iodine load more than 200,000-fold higher than the recommended daily intake.[2] While the normal thyroid gland can usually adapt to an excess iodine load, individuals with an underlying thyroid abnormality, such as a multinodular goitre, may develop hypo- or hyper-thyroidism.

Excess iodine inhibits thyroid hormone release (Wolff-Chaikoff effect), which is usually transient and 'escape' occurs.[3] Failure of escape results in iodine-induced hypothyroidism which may be temporary or permanent. Patients thought to be most at risk of iodine-induced hypothyroidism are those with underlying thyroid disease such as autoimmune disease or type 2 amiodarone induced thyrotoxicosis (reviewed in [4]).

Iodine-induced thyrotoxicosis (IIT) (Jod-Basedow phenomenon) can also be transient or permanent and is thought to be more common in those with underlying thyroid autonomy, such as patients with a multinodular goitre.[4] The elderly have also been proposed to be at increased risk of IIT.[5] Not only is this

population less tolerant to the effects of thyrotoxicosis, but IIT in the elderly is more likely to be undiagnosed due to the non-specific nature of the symptoms. Martin *et al.* reported 60 elderly patients with thyrotoxicosis in whom 23% had received iodinated contrast in the preceding 6 months.[5] Of particular relevance, however, is that the diagnosis of thyrotoxicosis was not suspected in 62% of those affected and five patients died with uncontrolled hyperthyroidism.[5]

While many case reports or small case series have been published reporting thyroid dysfunction following iodinated contrast, only a small number of prospective studies have been performed. Conn *et al.* studied 73 patients from an iodine sufficient area and identified two patients who became hyperthyroid and an additional four others who developed either an elevated FT_4 or suppressed TSH.[6] Seven of 101 patients developed subclinical hyperthyroidism after coronary angiography in a Turkish study,[7] a region previously shown to be iodine deficient.[8] A nested case-control study identified iodinated contrast as being associated with the subsequent development of hyper- and hypothyroidism in an iodine-sufficient area with the number needed to harm of only 23.[9] In contrast, Hintze *et al* identified only 2 new cases of iodine-induced hyperthyroidism from 788 unselected patients undergoing coronary angiography in an iodine-deficient area.[10] No underlying thyroid disease was identified in either of these patients.

New Zealand is an iodine-deficient area and also demonstrates borderline selenium deficiency.[11, 12] These two micronutrients are important in normal thyroid physiology. Currently there is no New Zealand data available on the

incidence of iodine induced thyroid dysfunction and international data may not be directly comparable due to both genetic variation and differences in availability of these two micronutrients.

The aims of this study were to:

1. Assess the incidence of iodine-induced thyrotoxicosis following the intravenous administration of iodinated contrast media used routinely in CT investigations
2. To determine whether IIT occurs more frequently in older patients (≥70 years) as compared to younger patients (<70 years).

Methods

Adult patients undergoing an elective, outpatient intravenous (IV) contrast-enhanced CT scan at Waikato Hospital, Hamilton, New Zealand, between 08/02/2013 – 08/07/2014 were invited to participate in the study. Exclusion criteria included: pregnancy, age less than 16 years, inability to give informed consent, use of thyroid replacement, anti-thyroid therapy or iodine-containing medications in the past 6 months, use of kelp tablets or other over-the-counter preparations containing iodine, or recent (within the past 6 months) iodinated contrast investigations (including angiography). Ethical approval for the study was granted by the Northern Y Regional Ethics Committee (NTY/12/02/019). Written, informed consent was obtained from all patients.

Following consent, baseline thyroid function tests (FT_4, FT_3, and TSH), thyroid autoantibodies (anti-thyroid peroxidase [anti-TPO] and anti-thyroglobulin [anti-TG]), and a fasting urine sample for urine iodine and creatinine values were collected prior to contrast administration. Due to financial constraints only a sample of 49 urine specimens underwent laboratory analysis. Follow up thyroid function tests were requested at four and eight weeks after the scan for each individual. The patient and/or their time point sample were excluded if further contrast was administered prior to the week eight blood test. FT_4, FT_3, and TSH were measured using a Roche Modular Analytics E170 immunoassay (Roche Diagnostics, Mannheim, Germany).

Omnipaque™ (iohexol) 300, Omnipaque™ 350 or Visipaque™ (iodixanol) 320 IV iodinated contrast media (ICM) was given depending on renal function and as per the radiology department protocol. CT images were then obtained on either the Siemens 256-slice dual-energy FLASH or Siemens 128-slice Edge scanner. In those patients who had imaging of the thyroid available, the scans were reviewed to assess thyroid size and the presence or absence of thyroid nodules. Thyroid volume was assessed using the thyroid/trachea index, where the maximum transverse diameter of each thyroid lobe were combined and compared with the maximum trachea diameter at that level.[13]

Hypothyroidism was diagnosed if the TSH level was elevated above the upper limit of the reference range. Hyperthyroidism was diagnosed if the TSH was below the lower limit of the reference range. Hyperthyroidism was further subdivided into subclinical if the free thyroid hormone levels were normal or

overt if they were elevated. Any patients who developed abnormal thyroid function tests were referred to the endocrinology service for a detailed assessment including bedside thyroid ultrasound and further management.

Statistical analysis was performed using STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) A p value of <0.05 was considered significant. Differences in TSH, FT_3 and FT_4 in all participants over follow up were calculated using within-subjects repeated-measures ANOVA. Comparisons between groups (age, gender and renal function) over follow up were calculated using between-subjects within subjects repeated-measure ANOVA.

Results

General

A total of 110 patients were initially identified as eligible for the study. Four patients were excluded due to not having had any post scan thyroid tests performed. An additional four patients received additional iodinated contrast within the first four weeks after the scan and were also excluded. The remaining 102 patients were included in the final analysis, 52 female and 50 male, with a mean age of 64.4 years (range 16 - 89 years). CT of the neck, chest, abdomen and/or pelvis was performed in 70 patients, kidney in 19, brain in 9, aorta in 6 and adrenal in 1. In 17 patients (17%) the scan request specifically included the neck. Several patients had multiple areas scanned e.g. neck and chest. Omnipaque 300 was given to 75 (76.5%) of patients, at a mean volume of 100 mL (range 75 – 135 mL). Overall, the mean total iodine load was 29,808 mg (range 16,000 – 40,500 mg).

Baseline Results

Baseline results for the group are shown in Table 1. Prior to iodinated contrast, three patients had abnormal TSH values: one with subclinical hyperthyroidism, (TSH 0.24mU/L [reference range 0.3 – 5mU/L]), and two with subclinical hypothyroidism (TSH values 5.78 and 8.11mU/L, respectively). All three patients had normal free thyroid hormone levels. Thyroid antibodies were elevated in 27 patients (28%) at baseline: 14 had elevated anti-TPO titres; 13 raised anti-TG; and both anti-TPO and anti-TG were elevated in 8 patients. Seventeen patients

(17%) patients had an eGFR ≤60mL/min, including one patient who developed subclinical hyperthyroidism.

Urine iodine was measured on 49 patients. One patient had a markedly elevated value (9104.8 umol/L) and on further enquiry was identified to have collected the sample following iodinated contrast. His result was therefore excluded from further analysis. The median urine iodine concentration was 0.9umol/L (range 0.2-2.6umol/L) with 4 participants (8%) having levels below 0.4umol/L. The World Health Organization defines a population as having no iodine deficiency if the median urine iodine level is 100-299ug/L (0.79-2.4umol/L) with <20% of the population having a level <50ug/L (0.4umol/L).[14]

Follow up results

Following the iodinated contrast scan, 90 patients completed both 4- and 8-week blood tests, on average at 30 days and 59 days, respectively. Seven patients completed only one blood test, at either week 4 or week 8. An additional five patients received further iodinated contrast between the 4- and 8-week blood tests. The 8-week results for these five patients were excluded from further analysis.

In the overall group, mean TSH levels dropped between baseline (TSH 1.78mU/L) and 4-weeks (TSH 1.58mU/L) with recovery back to baseline levels by 8-weeks (TSH 1.74 mU/L), p=0.01. Mean FT_3 levels increased between baseline (4.42pmol/L) and 4-weeks (4.55pmol/L), with a return to baseline by

8-weeks (p=0.04). Mean FT4 levels did not alter between baseline and 4- or 8-weeks (p=0.82). Comparison was also made between the two age groups: ≥70 years (n=51) and <70 years (n=51) at these time points with no significant differences seen between the two age groups. These results are shown in Table 2. There was no difference in TSH, FT4 or FT3 levels in those who had an eGFR ≤60mL/min and those who had an eGFR ≥90mL/min (p=0.18, p=0.16 and p=0.93, respectively).

Of the three patients with abnormal baseline TSH levels, the patient with a low baseline TSH had a persisting subnormal TSH at 4 and 8 weeks (0.28 and 0.18mU/L, respectively). At review, this patient had a normal thyroid assessment, including ultrasound, and TSH had normalised within 3 months of receiving ICM. Both patients with subclinical hypothyroidism prior to ICM administration remained subclinically hypothyroid at both week 4 and 8 weeks.

Following ICM two patients developed new onset subclinical hyperthyroidism with their free thyroid hormone levels remaining normal. Demographic and clinical details for these patients are given in Table 3. One of these patients (Patient A) had elevated anti-TPO antibodies at baseline and was identified to have an enlarged right thyroid lobe and underwent a diagnostic hemithyroidectomy to alleviate compressive symptoms. Histological examination demonstrated Hashimoto's thyroiditis and a 90mm follicular variant papillary thyroid carcinoma. The second patient (Patient B) had negative thyroid antibodies and a normal thyroid assessment, and thyroid function tests

normalised by three months post contrast ICM. No patients developed new onset hypothyroidism.

One patient had a low baseline FT_3 level, which had returned to normal on 4- and 8-week follow up bloods. Two patients developed a low FT_3 at 4 weeks and eleven patients at week 8 but none had an elevated TSH level. No patients developed abnormal FT_4 levels.

Thyroid imaging

Of the 102 participants, 63 (62%) had their thyroid gland included on the CT scan field, although in only 38 patients (37%) was the thyroid visualized in entirety with the remainder partially visualized (usually missing the upper few millimetres only). Of those 38 individuals, 13 (34%) demonstrated thyroid nodularity, with retrosternal thyroid extension in 4 (10.5%). Of those 25 in whom the thyroid was only partially visualized, imaging demonstrated nodularity in 10 patients and retrosternal thyroid extension in 6. Overall, 23/63 patients (37%) showed nodular thyroid disease and 10/63 (16%) had retrosternal thyroid extension.

The mean value for the transverse diameter of the thyroid glands visualised in entirety was 26.95mm (95% CI 24.96-28.94). Including the patients with a partially imaged thyroid gland the mean transverse diameter was 28.43 mm (95% CI 26.70-30.15). Measurements for the trachea showed a mean of 17.71mm (95% CI 17.03-18.39) in the fully visualized participants, which decreased to 17.41 mm (95% CI 16.73-18.10) when including the partially visualized participants. The mean thyroid/trachea index was 1.54 (95% CI 1.41-

1.67) in the 38 fully visualized thyroid individuals; this increased to 1.68 (95% CI 1.55-1.81) when the partially visualized thyroid glands were included. Twelve patients demonstrated an index greater than 1 standard deviation above the mean, 10 of whom also demonstrated thyroid nodularity and 6 retrosternal thyroid extension. Only four individuals demonstrated an index greater than 2 standard deviations above the mean. Of these three demonstrated a nodular thyroid and all had retrosternal extension present. The thyroid measurements are comparable to those calculated by Prince and Stark, who reported a mean thyroid gland diameter of 28.79mm, a mean trachea diameter of 19.97mm and a thyroid/trachea index of 1.46.[13]

Discussion

We have identified a low rate of iodine-induced hyperthyroidism in a cohort of patients undergoing CT scans with intravenous ICM. Of those with new onset thyroid dysfunction, the abnormalities were transient. No differences were seen in those aged <70 years compared to the 70 and over age group. Low FT_3 results developed in 13/102 patients at either week 4 or 8. This was not associated with an elevated TSH outside of the reference range and is unlikely to be clinically significant. This lowering of FT_3 is most likely to be due to the effect of the iodinated contrast on the Type 2 deiodinase, decreasing FT_4 to FT_3 conversion [15]. Similarly, while there was a statistically significant lowering of TSH and rise of FT_3 for the overall group, these changes were not clinically significant. As such, this study does not support the routine use of thyroid function testing following iodinated contrast in an unselected group of patients, even for those aged over

70 years. It has been hypothesised that patients with significant renal impairment may be exposed to a greater cumulative iodide exposure and therefore a greater risk of thyroid dysfunction, [16] however in this small study there was no significant difference in those with an eGFR <60mL/min compared to those with an eGFR >90mL/min.

No correlation was seen between thyroid volume and/or nodularity and abnormal TFTs, although only 62% of our study population had their thyroid gland at least partially included on the scan field, with only 37% viewed in its entirety. Similarly, no correlation was identified between age (>70 years of age) and thyroid volume or nodularity in our study population. The thyroid/trachea index however was demonstrated to be a fitting predictor of thyroid volume, with a high correlation with thyroid nodularity and retrosternal extension.

There were a number of limitations of this study. One limitation was that only a subset of participants had complete imaging of their thyroid available so we were not able to accurately determine the prevalence of underlying structural thyroid pathology in this cohort. In those 63 patients who did have their thyroid at least partially imaged a high rate of thyroid nodularity (37%) was identified. It is likely that this would be higher if thyroid ultrasonography were performed on all patients. This study does however suggest that even in a population with a high rate of background nodular thyroid disease, the rate of iodine-induced thyroid dysfunction is low. A spot urine iodine sample was collected in all patients and analysed in a subset. Apart from the patient who collected the urine sample following the ICM, no patients had elevated urine iodine levels at

baseline. A urine iodine level is the method recommended by the World Health Organization for assessment of the iodine status of a population.[14] Whilst New Zealand has traditionally been considered to be an iodine-deficient region, the urine iodine results in this subgroup were consistent with iodine sufficiency, however to get a true reflection of whether the population is truly iodine sufficient a larger group (>500 participants) is required. Recent assessment of New Zealand school children did suggest that New Zealand still has mild iodine deficiency.[17] A control group of patients who had not received iodinated contrast was not included in this study but previous work from our region has identified a low incidence of thyrotoxicosis at 0.2%.[18]

Whilst these unselected patients, including those with nodular thyroid disease, had a low rate of thyroid dysfunction following ICM, these findings may not apply to those with evidence of pre-existing thyroid autonomy i.e. TSH suppression or partial suppression. This particular group would be important to study as they may be at increased risk of IIT. One unforeseen difficulty in this study was patient recruitment. Due to one of our exclusion criteria being previous iodinated contrast in the preceding six months, most patients undergoing contrast-enhanced CT in our centre were not eligible for recruitment and this would need to be considered in the design of future studies.

Conclusion

In this relatively small prospective study from an iodine deficient region, 2% of patients developed new onset subclinical hyperthyroidism following a standard dose of iodinated contrast for CT investigations. Given the low incidence of

iodine-induced thyrotoxicosis, there is no indication for routine pre- and post-CT thyroid function testing in our region.

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Table 1. Baseline Laboratory Results

	Mean	95% CI	Reference range	N
TSH	1.78 mU/L	1.55, 2.0	0.3 – 5.0 mU/L	102
Free T4	11.4 pM	11.0, 11.8	12 – 22 pM	102
Free T3	4.42 pM	4.32, 4.52	3.6 – 6.5 pM	102
eGFR	76mL/min	72, 79	>90mL/min	101

Table 2. Subgroup comparisons

		Baseline			4 weeks			8 weeks			P-value
		n	Mean	95% CI	n	Mean change	95%CI	n	Mean change	95%CI	
TSH	All	102	1.78	1.55, 2.00	99	-0.18	-0.28, -0.07	93	-0.04	-0.18, 0.10	p=0.0133
	<70yrs	51	1.33	1.30,1.82	50	-0.19	-0.35, -0.04	46	0.05	-0.18, 0.28	p=0.1021
	>70yrs	51	2.01	1.65, 2.36	49	-0.15	-0.29, -0.02	47	-0.13	-0.29, 0.03	
	Female	52	1.89	1.52, 2.26	51	-0.18	-0.33, -0.03	46	0.02	-0.22, 0.26	p=0.7520
	Male	50	1.67	1.22, 1.67	48	-0.17	-0.31, -0.03	47	-0.10	-0.24, 0.04	
FT4	All	102	11.4	11.0, 11.8	99	0.14	-0.21, 0.49	93	-0.12	-0.49, 0.25	p=0.8240
	<70yrs	51	11.3	10.8, 11.9	50	0.01	-0.48, 0.57	46	-0.29	-0.92, 0.35	p=0.8150
	>70yrs	51	11.5	10.9, 12.1	49	0.29	-0.10, 0.69	47	0.05	-0.35, 0.44	
	Female	52	11.2	10.6, 11.7	51	0.32	-0.14, 0.78	46	0.03	-0.46, 0.52	p=0.9721
	Male	50	11.7	11.1, 12.3	48	-0.05	-0.58, 0.47	47	-0.26	-0.83, 0.30	
FT3	All	102	4.42	4.32, 4.52	100	0.23	0.07, 0.40	93	0.002	-0.20, 0.20	p=0.0418
	<70yrs	51	4.55	4.39, 4.70	51	0.30	0.07, 0.53	46	0.10	-0.22, 0.41	p=0.7622
	>70yrs	51	4.29	4.17, 4.41	49	0.16	-0.08, 0.39	47	-0.09	-0.35, 0.17	
	Female	52	4.37	4.24, 4.50	52	0.31	0.09, 0.54	46	-0.04	-0.30, 0.22	p=0.1997
	Male	50	4.46	4.31, 4.62	48	0.14	-0.10, 0.39	47	0.04	-0.27, 0.35	

Table 3. Clinical details of patients with new onset thyroid dysfunction

Case	Age yrs	preTSH mU/L	AntiTg IU/mL	AntiTPO IU/mL	wk4TSH mU/L	wk8TSH mU/L	Scan	Contrast	Volume mL	Iodine load mg	eGFR
A	45	1.63	5.5	352.3	0.03	0.83	Abdo/Pelvis	Omn 300	95	28,500	>90
B	89	0.45	3.9	0.7	0.2	0.19	Kidney & Urogram	Visi 320	100	32,000	53

Omn = Omnipaque; Visi = Visipaque