Clinical Thyroidology / Original Paper

European
Thyroid Journal

Eur Thyroid J
DOI: 10.1159/000367990

Received: July 4, 2014
Accepted after revision: September 1, 2014
Published online: ■■■

Patient Knowledge of Antithyroid Drug-Induced Agranulocytosis

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Key Words
Hyperthyroidism · Thyrotoxicosis · Agranulocytosis · Antithyroid drugs · Thionamide drugs · Questionnaire · Survey

Abstract
Background: Agranulocytosis is a serious side effect of antithyroid drugs. ***Objective:*** To ascertain the knowledge of patients and review the quality of information available on the internet. ***Methods:*** A questionnaire survey was performed for patients receiving antithyroid drugs. Patients attending endocrine clinics who were receiving antithyroid drug treatment (group A, n = 33) were interviewed. A further national cohort of patients (group B, n = 100) treated with antithyroid drugs, participated in an online survey. ***Results:*** 60.9% of responders were not aware of the common symptoms of agranulocytosis. 18.6% had never received any information about side effects. Of the 108 patients who recalled receiving information, 30% rated the quality as 'poor' or 'not good at all'. Structured interviews of group A patients revealed that almost half (45.5%, 15/33) had experienced symptoms that could be indicative of agranulocytosis, but only 53.3% (8/15) had a blood count checked. A review of 20 selected patient information internet sites revealed a significant variation in advice given to patients. ***Conclusions:*** Inadequate knowledge about agranulocytosis among patients receiving antithyroid drug treatment is common. The available information on the internet is variable and inconsistent.

Introduction

Hyperthyroidism affects approximately 1% of the adult population [1, 2]. Antithyroid drugs are commonly used to control hyperthyroidism [3, 4]. Assuming an incidence of Graves' disease in Europe of 21/100,000 per year [5], that the duration of treatment is usually 1 year, and that about 70% of patients are treated with antithyroid drugs, it can be estimated that about 110,000 patients receive antithyroid drug treatment at any one time.

One of the most serious side effects of antithyroid drugs is agranulocytosis. The frequency of agranulocytosis among users of antithyroid drugs is between 0.03 and 0.18% per annum [6–8]. Thus it is estimated that 30–200 episodes of agranulocytosis may occur in the Europe every year. Between 1963 and 2003, 19 fatalities due to antithyroid drug-induced agranulocytosis were registered

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in the UK [9], though this is likely to be an underestimate of the true incidence. Agranulocytosis usually manifests with a fever or sore throat. It is standard practice to advise patients about this side effect and to instruct them to stop the medication and seek urgent medical advice and a blood test, should they develop symptoms suggestive of agranulocytosis.

Patient education regarding the serious side effects of antithyroid drugs is an important part of the management of patients receiving this treatment. Previous audits in the UK on the level of information recalled by patients on side effects of antithyroid drugs indicated that only 56–70% would take appropriate action in the event of symptoms suggestive of agranulocytosis [10, 11], though information on this topic remains sparse in the literature.

The aims of this study were (a) to gain further information about the knowledge of patients being treated with antithyroid drugs about agranulocytosis and their views and experience about the information received on this side effect; (b) to explore how patients being treated with antithyroid drugs might react to a hypothetical scenario of agranulocytosis, and (c) to review the quality of information available to patients on the internet about antithyroid drug-induced agranulocytosis.

Methods

A questionnaire on side effects of antithyroid drugs was used to collect data from patients (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000367990). The questionnaire was piloted initially in a small number (n = 5) of patients and revised to improve the ease of completion and clarity of questions. Two groups of participants were targeted: consecutive patients attending endocrine clinics in a single centre who were receiving antithyroid drug treatment (group A, n = 33), and responders to a UK-based on-line survey (group B, n = 100). The questionnaire used for group B was a simplified version of that used for group A. This approach allowed access to a broad population of patients from different geographical areas of the UK (group B) as well as to data derived from a detailed face-to-face structured interview of a smaller group of patients (group A). To recruit group B participants, a call was put out electronically by the British Thyroid Foundation to its members and the general public. SurveyMonkey (www.surveymonkey.com) was used to collect the data from group B. No patient from group A participated in the web-based survey. Group B participants self-selected for either currently receiving (n = 78), or having previously received antithyroid drugs (n = 22). The data from groups A and B were pooled for some of the analyses. In addition to filling the same questionnaire as group B, group A participants were asked further questions during a structured interview. The interview included a case scenario designed to ascertain the response to symptoms of agranulocytosis with a three-step increase in complexity.

The study included a 'Google.co.uk' search on patient information about antithyroid drugs using the search term 'antithyroid drugs and patient information'. The top 20 relevant sites were selected for further analysis. The selection criteria were: inclusion of information on side effects of antithyroid drugs; source from National Health Service or professional and patient-led organisations; drug manufacturers and other sources judged by the authors to be reliable. The Medicines and Healthcare Products Regulatory Agency (MHRA) Best Practice Guidance on Patient Information leaflets was used to score the quality of patient information on the internet [12].

The patient information leaflets were checked for readability using the software tool http://www.online-utility.org/english/readability_test_and_improve.jsp to calculate the Flesch-Kincaid Grade Level (FKGL).

A PubMed literature search with the term 'agranulocytosis and antithyroid drugs' was performed. All relevant articles (original articles, case series, case reports) written in English between 1999 and 2013 were reviewed and data on symptoms of agranulocytosis and clinical diagnoses of source of infection were noted. Two-sample t tests and χ^2 tests were used to analyse the data.

Results

The baseline clinical characteristics of patients are shown in table 1. The duration of treatment with antithyroid drugs of the clinic-based patients (group A) was slightly shorter than that of participants from the web-based survey (group B), otherwise baseline characteristics were similar. Response rates to individual questions were high with a median of 96.5% (75–100%).

Table 1. Baseline characteristics of participants in the endocrine clinic (group A) and web-based survey (group B)

	Group A	Group B	p
Participants, n	33	100	
Mean age ± SD, years	50.9±16.3	46.9±12.8	0.20
Females, %	84.8	95.8	0.085
Participants taking antithyroid drugs at the time of the survey, n	33	78	0.05
Median duration (range) of therapy of current antithyroid drug users, months	8 (0.25–48)	10 (0.5–244)	<0.005

Pooled Questionnaire Data for Groups A and B (table 2)

One or both of the two commonest symptoms of agranulocytosis (fever, sore throat) were correctly identified by 39.1% (52/133) of responders. The majority of responders (81.4%, 92/113) had received information about side effects from health professionals with (34.5%, 39/113), or without (46.9%, 53/113), additional information in leaflet form handed to them by the health professional; 18.6% (21/113) of responders could not recall any information being given to them by health professionals on side effects, and this subgroup of patients accessed information by themselves through the internet or drug packet insert. In 34.2% (37/108) of cases a reminder about side effects was given by health professionals during follow-up. Confidence about knowledge of side effects was low in 37.2% (48/129) of cases. The quality of information received was rated as 'poor' or 'not good at all' by 30% (39/130) of responders. Just under half (44.6%, 58/130) of participants thought that the amount of information they had received was too little. The majority of participants (57.4%, 70/122) expressed a preference for receiving information on side effects during a consultation with a health professional.

Additional Data from Extended Interview of Group A (table 3)

Since starting antithyroid drugs, 45.5% (15/33) of patients had experienced 31 separate episodes of symptoms suggestive of agranulocytosis. Only 54.3% (8/15) of patients had a blood count. None required additional action. Patients were asked about the action they would take if they developed a sore throat whilst taking their medication. The responses were: routine appointment with their GP by 42.4% (14/33), seek medical advice urgently by 36.4% (12/33), or, carry on as normal by 21.2% (7/33). Of those who responded that they would make a routine appointment with the GP, only 64.3% (9/14) would stop

Table 2. Responses to questionnaire survey (pooled data from groups A and B)

Responses to questionnaire	Responders
Aware of symptoms of agranulocytosis (fever/sore throat)	39.1% (52/133)
Source of information on side effects of antithyroid drugs	
Consultation with health professional	81.4% (92/113)
No information from health professional	18.6% (21/113)
Reminder(s) about side effects received during follow-up	34.2% (37/108)
Confidence about knowledge of side effects of antithyroid drugs	
Not confident at all	19.4% (25/129)
Unsure	17.8% (23/129)
Slightly confident	13.0% (17/129)
Confident	31.7% (41/129)
Very confident	17.8% (23/129)
Rating of quality of information about side effects of antithyroid drugs by participants	
Not at all good	17.7% (23/130)
Poor	12.3% (16/130)
Okay	27.7% (36/130)
Good	24.6% (32/130)
Excellent	17.7% (23/130)
Amount of information received about side effects of antithyroid drugs	
Too little	44.6% (58/130)
About right	52.3% (68/130)
Too much	3.1% (4/130)
Preferred means of receiving information about side effects of antithyroid drugs	
Letter	19.7% (24/122)
Text	1.6% (2/122)
E-mail	6.5% (8/122)
Telephone	1.6% (2/122)
Consultation with a health professional	57.4% (70/122)
Multiple means	13.2% (16/122)

Table 3. Group A participants (n = 33) who were current antithyroid drug users were asked to respond to a case scenario

1.	'Imagine that you get a sore throat while on the antithyroid medication. What would you do next?'	
	Routine appointment to see the GP	42.4% (14/33)
	Make appointment to see the GP and stop taking the tablets	64.3% (9/14)
	No immediate action	21.2% (7/33)
2.	'Suppose that 24 h later, your sore throat is no better and you rang your GP to make an appointment. The receptionist has given you an appointment in 5 days. What would you do next?'	
	Accept appointment	18.2% (6/33)
	Accept appointment and continue tablets	66.7% (4/6)
3.	'Suppose that on the following day your sore throat is worse and you are still taking the antithyroid medication. What action would you take?'	
	Seek immediate medical advice	100% (33/33)
4.	'If you could not get immediate medical advice and you were still on antithyroid medication would you stop now?'	
	No	39.4% (13/33)
5.	'Suppose that you managed to get the appointment with your GP forward by a day. You wake up on the following day and you still have a sore throat, and you feel worse. Your appointment with your GP is in 2 days and it is Saturday and the surgery is closed. If you are still on the tablets would you stop?'	
	No	27.3% (9/24)
6a.	'If instead of a sore throat you had fevers, would you have acted differently?'	
	Yes	54.5% (18/33)
6b.	'If 'yes', is it more or less likely that you would have insisted to be seen early by a doctor?'	
	Less likely	66.7% (12/18)
7a.	'If instead of a sore throat you several painful mouth ulcers, would you act differently?'	
	Yes	42.4% (14/33)
7b.	'If 'yes', is it more or less likely that you would have insisted to be seen early by a doctor?'	
	Less likely	21.4% (3/14)

taking antithyroid drugs in the meantime. In response to the case scenario that an appointment to see the GP was offered in 5 days, 18.2% (6/33) of patients accepted this and 4/6 (66.7%) continued to take antithyroid drugs. In response to the case scenario that on the following day the symptoms were worse, 100% of patients sought immediate medical advice; however, 39.4% (13/33) of patients responded that they would continue taking the antithyroid medication. The scenario then of a further worsening of symptoms and an inability to access medical attention, led to 72.2% (24/33) of patients discontinuing the antithyroid medication, while the remaining 9/24 (27.8%) stated that they would continue taking antithyroid drugs.

With regard to symptoms of agranulocytosis other than a sore throat, 54.5% (18/33) patients stated they would act differently if the symptom was fever and 42.4% (14/33) would act differently if they had multiple painful mouth ulcers. In 66.7% (12/18) and 21.4% (3/14) of cases respectively, patients said they were less likely to seek medical attention than if they had a sore throat.

Review of Selected Internet Sites

The internet search yielded about 72 million results. Of these, the first 100 were screened. Twenty sites (online suppl. table 2) were selected as being most relevant. Sore throat was quoted as a symptom of agranulocytosis by all 20 websites; three websites specified that the sore throat had to be 'severe'. Fever was mentioned in 85% (17/20), one specified that the fever had to be 'unexplained' and one that the temperature had to be >37.5°C. Mouth ulcers were mentioned by 80% (16/20) of websites. With regard to advice about what action should be taken by patients with symptoms suggestive of agranulocytosis, 65% (13/20) advised stopping the medication. Seeking advice

Table 4. Frequency of symptoms of antithyroid drug-induced agranulocytosis in 80 patients reported in the medical literature between 1999 and 2013 and frequency of symptoms mentioned in the 20 websites containing patient information material

Symptoms	Case reports, %	Web-based patient information, %
Fever	93.75	85.7
Sore throat	68.75	100
Fever and/or sore throat	100	100
Chills	21.25	0
Diarrhoea	11.25	0
Myalgia	10	0
Cough	8.75	7.1
Rash	7.5	14.2
Mouth ulcers	5	78.6
Abdominal pain	5	0
Nausea/vomiting	5	0
Headache	5	0
Rhinorrhoea	5	0
Malaise	3.75	14.2
Dysuria	1.25	0
Tiredness	1.25	7.1
Palpitations	1.25	0
Dysphagia	1.25	0
Arthralgia	1.25	0
Coryza	1.25	7.1

from a health professional immediately was recommended by 95% (19/20) of websites. The level of detail on how to access immediate medical advice varied from very sparse ('see a doctor urgently'), to very detailed. Accident and Emergency, or Casualty, were mentioned in 30% (6/20) of websites. Readability (based on Flesch Kincaid Grade level) varied between 7.71 and 17.49.

Review of Reported Cases of Antithyroid Drug-Induced Agranulocytosis in the Literature

Review of the literature of reported cases of agranulocytosis between 1999 and 2013 identified 80 cases where the presenting symptoms were described [13–37]. Fever (93.8%), sore throat (68.7%) and chills (21.2%) were the commonest presenting symptoms. Fever and/or sore throat were recorded in 100% of cases. Fever was defined in most cases as a temperature >37.5°C. The commonest clinical diagnoses (when specified) were pharyngitis or tonsillitis (86.4%), followed by pneumonia (9.1%). Despite some symptoms being relatively common in the agranulocytosis literature (chills 21.25%, diarrhoea 11.25%, myalgia 10%), none of the 20 patient information sites mentioned them. Conversely, mouth ulcers, a relatively uncommon symptom in the agranulocytosis literature (5%) featured as a symptom in 78.6% of the patient information sites (table 4).

Discussion

This survey has revealed deficiencies in patient knowledge about side effects of antithyroid drugs. The majority (60.9%) of participants did not know the symptoms of agranulocytosis; 18.6% stated that they had received no information at all by professionals. These patients sought information either on the internet or relied on the drug packet insert. The responses also indicated that often the quality and amount of information received was inadequate. There was confusion as to the relative importance of different symptoms of agranulocytosis (sore throat, fever, mouth ulcers), and each of these symptoms had a different impact on action taken for a significant proportion of participants. Repetition is key to retaining information, yet reminding patients of the side effects of antithyroid drugs by health professionals was claimed to have been infrequent (34.2%).

The extended interview of group A identified further deficiencies in patient education. Almost half (45.5%) of the patients had experienced symptoms suggestive of agranulocytosis, yet a blood count was performed only in 53.3% of affected cases. The case scenario unravelled that 21.2% of patients would take no action in the event of developing a sore throat. Many patients (42.4%) accepted a routine GP appointment, which may have introduced a delay in diagnosing and treating agranulocytosis. The most recent data from NHS England on waiting times for GP appointments [38] indicate that only a third of patients were able to actually see or speak to a health professional on the same day as they initially contacted the surgery. This highlights the difficulties that patients with agranulocytosis may face in accessing professional advice through the primary care route. In contrast, patients at risk of chemotherapy-induced neutropenic sepsis benefit from a well-defined pathway [39]. There was reluctance among participants to discontinue antithyroid medication in the face of deterioration in symptoms.

Limitations of this study include a small sample population, potential lack of reliability associated with patient surveys and selection bias (particularly for the web-based survey) heterogeneity of the subjects (current versus past use of antithyroid drugs and how long they have been taking medication) recollection bias, and different providers. The demographics (age, sex), however, were similar to that ex-

pected from a population of patients being treated with antithyroid drugs for hyperthyroidism, and some of the findings of this survey were similar to audits conducted in other UK centres [10, 11]. It is therefore reasonable to expect that the findings of this survey are likely to reflect the wider population of patients being treated with antithyroid drugs. Mortality from antithyroid drug-induced agranulocytosis is very low. Nonetheless, it is good practice to educate patients taking antithyroid drugs about agranulocytosis. Such information ought to be evidence-based, clear and consistent. The internet search showed significant inconsistencies. The quality of the information was relatively poor (median score based on Best Practice Guidance for patient information leaflets [12], 10, range 4–15, maximum score 20) and readability scores varied between 7.71 and 17.49 (optimal readability score is considered to be about 13) [40].

The findings from this study lead to the conclusion that there is a need for a robust strategy in order for antithyroid drug-induced agranulocytosis to be recognised early by patients and appropriate action to be taken. This has to be based on uniform, authoritative, high-quality patient information about side effects. The advice about what action to take if the threshold is reached, should include: (a) stopping the antithyroid medication immediately; (b) reassurance that stopping the medication for 1–2 days will not result in any danger; (c) seeking medical advice immediately, i.e. on the same day; (d) persevering in seeking medical advice if unable to speak to or see the GP on the same day; (e) insisting on having a blood count if the health professional does not offer a blood test; (f) advising patients that if they have experienced a 'false alarm' in the past, that must not make them reluctant to take appropriate action again if they develop symptoms suggestive of agranulocytosis in future.

In order to achieve an adequate level of patient knowledge and confidence, the minimum requirement would appear to be for information to be delivered by a professional during a consultation, and be reinforced by written material and reminders during subsequent consultations. Given that the highest risk of agranulocytosis is in the first 3 months after commencing antithyroid drug medication, efforts to educate and remind patients are best concentrated in this initial phase of treatment.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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