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How do paediatricians use and monitor anti-thyroid drugs in the UK? A clinician survey

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Summary

Objective: We aimed to document current practice in the medical management of paediatric hyperthyroidism in the UK and compare to international recommendations.

Design: A 27 question online survey distributed via an electronic newsletter in August 2018.

Participants: Responses from 48 members (11%) of the British Society for Paediatric Endocrinology and Diabetes.

Measurements: Information about anti-thyroid drug (ATD) preference, treatment duration, monitoring of full blood count (FBC), management of neutropaenia, agranulocytosis screening and patient education.

Results: Carbimazole is favoured by 98% of respondents and a 'dose titration' regimen preferred over 'block and replace' (65% versus 29%). TRAbs (Thyroid Stimulating Hormone Receptor Antibodies) are used for diagnostic purposes by 85% and by 33% to look for evidence of disease remission. The majority (81%) treat for a minimum of 2 years before considering a trial off ATD. All respondents reported that they 'always/usually' warn their patients about the risk of agranulocytosis before starting ATD, but written information is 'rarely/never' provided by 63%. Sore throat (98%) and fever (92%) are the most commonly cited symptoms used to alert a patient to possible agranulocytosis. FBC is measured prior to treatment by 65% and measured periodically during treatment by 70%.

Conclusions: The management of paediatric hyperthyroidism with ATDs in the UK is not consistent with all international recommendations because a block and replace ATD regimen remains widely used. TRAbs are utilised at presentation, but under-used for detecting disease remission. National consensus guidelines and written patient information may refine the management of paediatric patients on ATDs.

Key Words

Hyperthyroidism, Immunosuppression, Graves disease, Carbimazole, Thionamide

Conflict of Interest

The authors report no conflict of interests that could be perceived as prejudicing the impartiality of the research reported.

Data Availability Statement

The data that support the findings of this study are openly available in "figshare" at https://doi.org/10.6084/m9.figshare.7962839.v1 and https://doi.org/10.6084/m9.figshare.7962860.v1.

1 Introduction

The incidence of hyperthyroidism in children in the UK and Ireland is 0.9 per 100,000 and is due to underlying Graves' disease in 96% of cases.[1] Medical treatment consists of thionamide anti-thyroid drug (ATD) using Carbimazole (CBZ), its active metabolite Methimazole, or Propylthiouracil (PTU). Only CBZ and PTU are available in the UK. The United States Food and Drug Administration released a warning in 2010 regarding the increased risk of hepatotoxicity associated with PTU in children and, as a result, CBZ is recommended as first-line treatment, with the exception of the first trimester of pregnancy.[2-6] ETA (European Thyroid Association) and ATA (American Thyroid Association) guidelines advise on treatment for adults and children. Both advocate the use of CBZ over PTU in children. The ATA recommend a treatment duration of 12-24 months, and the ETA a treatment duration of 36 months prior to stopping ATD therapy in children to check for remission.[2,3] JTA (Japanese Thyroid Association) guidelines are paediatric specific and recommend treatment with Methimazole for a duration of 18-24 months.[4]

ATD therapy typically involves either titrating the dose of ATD until the patient becomes euthyroid (dose titration, DT) or maintaining a high dose of ATD to suppress endogenous thyroid production and then replacing thyroid hormone with Levothyroxine (block and replace, BR). BR may require fewer hospital visits and blood tests whilst DT is associated with fewer ATD side-effects because of the lower ATD dose.[1,3,7] ETA guidelines do not advocate one treatment regimen over the other but the ATA recommend DT. JTA guidelines recommend avoiding BR, citing the 2010 Cochrane Collaboration review that identified an increased risk of adverse reactions with this treatment strategy when compared to DT.[4,7] However it has been highlighted that some of the studies included in the Cochrane review, and in the BR section of the analyses, used an ATD dose that was much higher than routinely used in clinical practice.[8] The Cochrane review also focused on the use of ATD in the context of adults and not the management of children and adolescents.

A rare but potentially fatal side effect of ATD therapy is agranulocytosis, defined as an absolute neutrophil count (ANC) of < 0.5 $x10^9$/L.[9] It is important that patients are aware of the need to have their full blood count (FBC) checked when they experience symptoms suggestive of agranulocytosis. Symptoms are non-specific, most commonly fever and sore throat in adults presenting with agranulocytosis secondary to ATDs.[10] Although it is recommended that patients are provided with written information about the risk of agranulocytosis, international guidelines do not specify symptoms which should trigger consideration of agranulocytosis or measurement of an FBC.[2,3] Recommendations in the UK suggest that three measures should be taken to manage the risk of

agranulocytosis: Patients should be asked to report symptoms of infection; a white blood cell count should be performed when there is clinical evidence of infection; and CBZ should be stopped promptly if there is clinical or laboratory evidence of neutropaenia.[11]

We set out to establish the current approach to ATD use in children in the UK. We also sought to understand how the risk of agranulocytosis is managed, exploring how clinicians might respond to blood tests demonstrating a low white cell count. We also explored clinician's use of TRAb (Thyroid Stimulating Hormone Receptor Antibody) measurement and the typical duration of ATD treatment in children with hyperthyroidism.

2 Materials and Methods

We reviewed the NICE 'Important Safety Information' for Carbimazole,[11] and the advice pertaining to safe prescribing of ATDs within international guidelines.[2,4] We then developed 27 questions that examined both adherence to published advice and the use and interpretation of related diagnostic tests, and compiled these into an online survey using 'Google Forms' (Google Drive Office Suite, Alphabet inc., Mountain View, CA, USA). We advertised the survey in the BSPED (British Society for Paediatric Endocrinology and Diabetes) newsletter e-mailed to all members in July and August of 2018, with a subsequent follow up email designed to boost the response rate. Respondents could choose to remain anonymous if preferred. The questions were multiple choice but 13 of the questions also included an option for free text. The full list of questions in the survey can be found at goo.gl/forms/7gbi8MnV6uZ7Umyg2.

The first seven questions sought demographic data about the respondent, the service that they work in as well as establishing whether a hyperthyroidism guideline was in use. Three questions elicited their ATD of choice, whether they had a preference for DT or BR and whether they perform an FBC prior to ATD initiation. Respondents were then posed six questions exploring whether patients are warned about agranulocytosis, whether this includes written patient information, whether the warnings are repeated at follow up and whether there is a systemic warning system in place to remind clinicians to discuss the risk of agranulocytosis. We further explored the management of agranulocytosis with two questions pertaining to how patients are taught to recognise and react to agranulocytosis, and a question regarding the clinicians' actions should they be confronted with a range of low neutrophil counts. The following three questions explored the use of TRAbs and other factors that might influence the length of ATD

treatment, with four further questions about the experience of the respondent within paediatric endocrinology and how many cases of agranulocytosis or hepatic impairment they had encountered secondary to ATD use. We used conditional branching within the survey to divert respondents away from questions that were not relevant to them. The survey remained open to responses for 6 weeks.

We used descriptive statistics to quantify responses to each question, calculating the percentage of responses to each question using the number of respondents to that question as the denominator. We collated and analysed data within Microsoft Excel (MSO 16, Microsoft Corporation, Redmond, WA, USA).

As the study was a survey on healthcare provision and did not collect individual patient information, research ethics approval was not required.

3 Results

3.1 Demographics

The BSPED committee sent the newsletter to 437 members, of whom 266 are medical consultants. We received a total of 48 responses (11%), of which 32 were from clinicians in a tertiary centre and 16 from a secondary centre. Respondents comprised 30 consultant paediatric endocrinologists, 16 consultant paediatricians with a special interest in endocrinology, and two paediatric doctors in training. Contact details left voluntarily by half of respondents (24/48) revealed that half of the major conurbations in England and Wales with tertiary endocrine units were represented by these individuals alone..

Respondents collectively reported 519 years of experience in paediatric endocrinology, with 63% (30/48) of respondents having over 10 years of experience in the field and only three respondents reporting less than two years of experience in the field. The majority (54%, 26/48) of respondents had never encountered a patient with agranulocytosis secondary to ATD use, whilst 44% (21/48) had seen one or two cases, and one individual three or four cases.

3.2 Management of Hyperthyroidism

Guidelines for the treatment of hyperthyroidism are used by 21% (10/48) of respondents. Five use a local trust guideline, one a local network guideline, and four a national or international guideline. CBZ is the first line ATD used by 98% (47/48) of respondents, with 65% (31/48) reporting a preference for DT, 29% (14/48) for BR and 6% (3/48) reporting no preference (Figure 1).

TRAb's are used to assist diagnosis by 85% (41/48) of respondents, although fewer employ them to predict prognosis (46%, 22/48), check for remission (33%, 16/48), or monitor treatment (8%, 4/48) (Figure 2). Length of time on treatment is typically used to gauge when to trial patients off treatment (94%, 45/48), although where the young person is in relation to important educational milestones, such as examinations, is also frequently considered (79%, 38/48). A majority of 81% (39/48) of respondents consider two years as the minimum duration of treatment prior to a trial off ATDs, while six respondents reported a year or less and one reported a minimum of five years.

3.3 Agranulocytosis

All respondents reported that they 'always' or 'usually' warn their patients about the risk of agranulocytosis before starting ATD treatment, with 70% (32/46) reporting they then discuss the risk of agranulocytosis 'usually' or 'at every appointment' during follow up. However, written information about agranulocytosis is 'rarely' or 'never' provided by 63% (30/48). When educating patients about how to recognise a possible case of agranulocytosis, the symptoms that clinicians mention most frequently to patients are sore throat (98%, 47/48), fever (92%, 44/48) and oral ulcers (44%, 21/48).

Prior to starting a patient on an ATD, 88% (42/48) measure an FBC. On follow up 28% (13/46) check an FBC every time they measure thyroid function and 65% (30/46) 'on an *ad hoc* basis' (Figure 3). Responses to a question seeking the definition of agranulocytosis were equally split between correctly identifying this as an absolute neutrophil count (ANC) of $< 0.5 \times 10^9$/L (40%, 19/48) and the same proportion defining it as an ANC < 1.0 (40%, 19/48). When asked how to manage a low neutrophil count, 35% (17/48) would admit a patient with an ANC $< 0.5 \times 10^9$/L to hospital, whilst 54% (26/48) would advise stopping the ATD and rechecking the FBC the next day as an outpatient. The management of a low neutrophil count was dependent upon the absolute neutrophil number with 8% (4/48)

stopping the ATD at a neutrophil count < 2.0 x10^9/L and 90% (43/48) stopping the ATD at a neutrophil count < 0.5 x10^9/L (Figure 4).[12]

Discussion

This is the first nationwide clinician survey studying the current approaches to the management of hyperthyroidism in children in the UK. Previous surveys of adult clinicians have shown international variation in the management of hyperthyroidism,[13,14] but preferences around the use of ATDs in children are unknown. The fact that such a substantial proportion of the large conurbations in the UK were represented by the respondents who highlighted their place of work leads us to believe that this survey is a meaningful representation of current UK endocrine practice.

We identified a preference among clinicians to use the DT approach to ATD administration rather than BR, which is in keeping with a 2013 European survey into adult practice.[13] Level 1 evidence of superiority of one ATD regimen over the other is lacking in paediatric practice. A Cochrane review in 2010, involving primarily adult patients, found relapse rates to be similar with both regimens, but a higher rate of side effects when using BR.[7] A BR regimen may have the advantage of necessitating fewer trips to the outpatients department, but the disadvantage of an extra medication burden for the patient,[16] and the increased rate of side effects has led the ATA to suggest avoiding this approach.

Most respondents (85%) use TRAbs to aid diagnosis of Graves' disease, which have been shown to shorten time to diagnosis and reduce management costs.[17] TRAbs are also recommended by the ATA and ETA to assist in predicting the likelihood of remission and to inform on the decision to wean ATD dose. Adult remission rates of over 80% are reported in cohorts with low or undetectable TRAbs compared to 20-30% in cohorts that have persistently elevated TRAbs.[18,19] Whilst 33% of respondents are monitoring TRAbs for this indication, there is the potential to increase their use to improve remission rates in the paediatric cohort. UK clinicians continue patients on ATDs for two years prior to a trial off treatment, longer than the 12-18 months suggested in the ATA guidelines, but less than the 3 years suggested by the ETA and 5-10 years by the JTA.[2-4]

Whilst clinicians in this survey report consistently informing patients about the risk of agranulocytosis, the proportion who regularly provide written information, as advised in both ATA and ETA guidelines, is low (37%).

Although advised, neither the ATA nor ETA provide a standardised patient information leaflet. In the UK, the Medicines for Children partnership programme have produced a patient information leaflet entitled 'Carbimazole for hyperthyroidism'.[20] This is over 1500 words long and, whilst informing patients about the risk of agranulocytosis, does not instruct them beyond 'contact your doctor straight away'. The British National Formulary, under 'important information about Carbimazole', states that CBZ should be stopped pending an FBC should the patient experience symptoms and signs of infection.[11] There is evidence that supplying patient information leaflets about medication increases patient knowledge about side effects as well as improving patient satisfaction.[21] We postulate that a short, simple patient information leaflet would increase the proportion of families and patients receiving and comprehending written information about CBZ. The leaflet would aim to increase awareness of agranulocytosis, with specific guidance to stop ATD therapy pending an FBC if symptoms of fever, sore throat or oral ulcers occur. These are the most frequent symptoms associated with agranulocytosis secondary to ATD use.[10]

Agranulocytosis is not the only side effect of CBZ but it is unique in combining frequently experienced and commonly innocuous symptoms such as sore throat and fever with a potentially fatal outcome. Pancreatitis has recently been highlighted as a recognised side effect,[22] alongside the risk of liver dysfunction or vasculitis.[2] We believe that these conditions have presenting features more likely be recognised as potentially pathological by patients or carers.

ATA and ETA guidelines recommend a more conservative approach to laboratory proven agranulocytosis than was demonstrated by the clinicians responding to our survey. Whilst 90% of respondents would stop the ATD with an ANC < $0.5x10^9$/L, only 35% would admit to hospital. It is important to note that rates of death in children with agranulocytosis secondary to ATD have been shown to be as high as 4%,[23] and thus treatment with intravenous broad-spectrum antibiotics is recommended.[24] However, we are wary of drawing too significant a conclusion from survey data into hypothetical patient management decisions, particularly as the option to discuss blood results with an expert in the field (i.e. a haematologist) was not available in our multiple choice questions.

In this survey, 70% of respondents reported they check an FBC with some degree of regularity. Routine monitoring of FBC for patients taking ATDs was considered unnecessary by the WHO (World Health Organisation) in 1999 due to the often abrupt onset of agranulocytosis.[25] This advice is reflected in ETA and ATA guidelines,[2,3] although JTA guidelines advise undertaking regular monitoring of white cell count during the first 3 months of treatment.[4] This timescale is consistent with data from UK reports of adverse drug reactions in adults prescribed CBZ showing a median onset of agranulocytosis of 31 days (range 14-105)[26], although cases have been described that have occurred

up to 11 years after the start of treatment.[27] Checking a FBC prior to the start of treatment, carried out by 88% of our respondents as recommended in ATA guidelines, can help to determine whether a low white cell count is due to ATD therapy or the disease itself. There is an association between untreated Graves' disease and the development of neutropenia, a finding more common in non-Caucasian patients and those with higher serum thyroid hormone levels.[28]

We recognise that our survey has limitations. Online clinician surveys are reported to garner a typical response rate of less than 20%,[15] and whilst our response rate of 11% is low in the context of the entire membership of the BSPED, this should be considered within the context of a membership that includes allied health professionals and a large proportion of clinicians who manage children with diabetes rather than endocrine conditions. A response rate of 40% has previously been demonstrated in another UK survey of Thyroid disease[29], but only within targeted email requests to consultants known to have an interest in the disease. Some BSPED members will be from small units with no recent experience of managing hyperthyroidism, or practice mainly or exclusively with patients with diabetes. In the case of some units, we know that one BSPED member responded on behalf of the team on the basis that they were representing their departmental strategy. Selection bias may have influenced the results with those with an interest in thyroid disease being more likely to respond and thus disproportionately reporting preferences made by specialists within the field. Recall bias may have influenced such a high proportion of respondents (100%) reporting that they always or usually discuss the risk of agranulocytosis with patients/carers. A local audit of patient notes in Sheffield revealed only 50% (7/14) of consultations where an ATD was initiated included documentation about the risk of agranulocytosis, and no documentation that patients were informed to stop the drug should it be suspected.[30] Knowledge of adult patients about the risk of agranulocytosis secondary to ATDs has been shown to be poor despite the information being verbally delivered by clinicians,[31] reinforcing the importance of providing this information in the written form.

In conclusion, this survey has shown that choice of ATD and duration of treatment by clinicians in the UK is consistent with current international recommendations, although a substantial proportion of children are still managed using a BR regimen despite the ATA guideline advising against this practice. The outcome of a UK randomised trial comparing biochemical control in young patients managed with either BR and DT is expected imminently and may help to guide and refine clinical practice further.[32] The measurement of TRAbs to aid diagnosis is a common practice but under-utilised in relation to detecting likelihood of disease remission and hence the timing

of ATD cessation. It appears that the majority of clinicians are managing hyperthyroidism without a guideline, perhaps contributing to the variation in practice demonstrated, and unable to backup verbal advice about agranulocytosis with written information. Patient education is at the heart of patient safety and it seems timely that a national guideline and patient information leaflet to support the management of paediatric patients on ATDs is considered.[24]

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Figure 1: Preference for Anti-Thyroid Drug Treatment Regimen

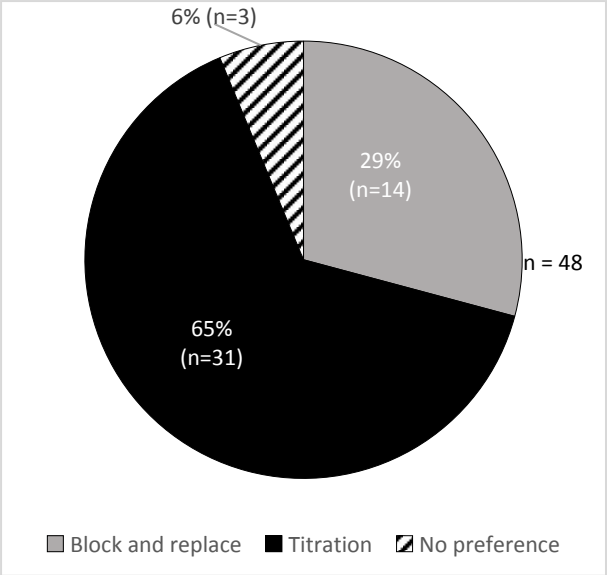
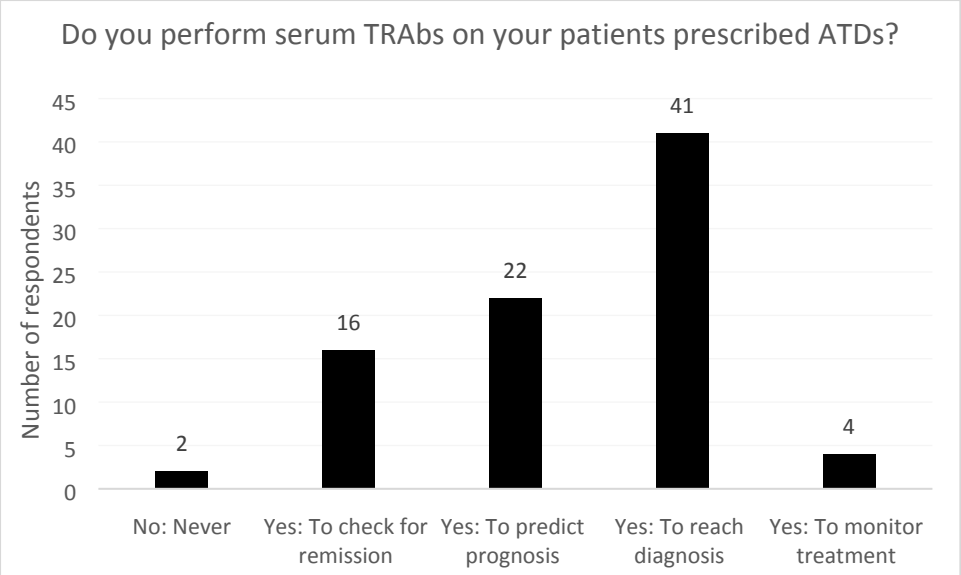
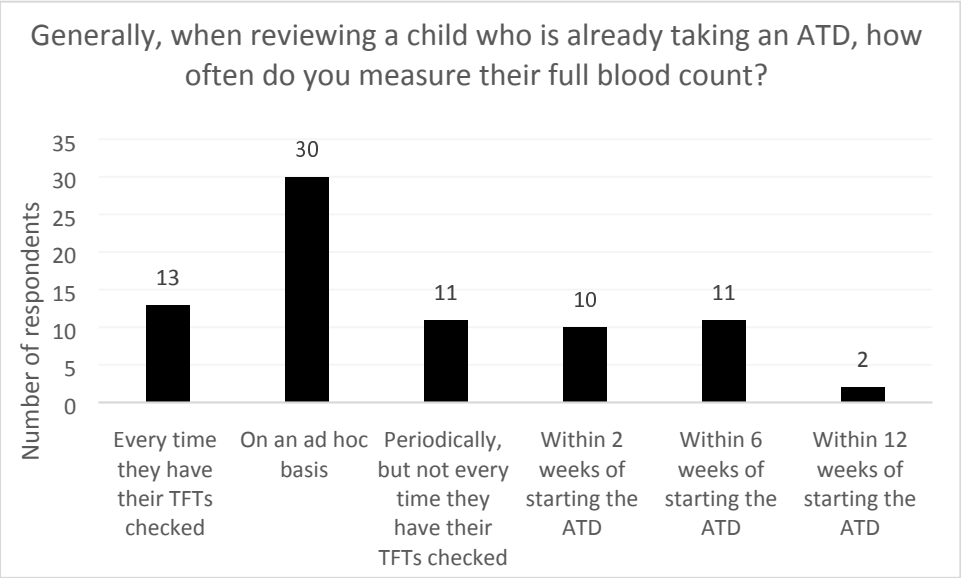


Figure 2: The Measurement of TRAbs in relation to ATD treatment



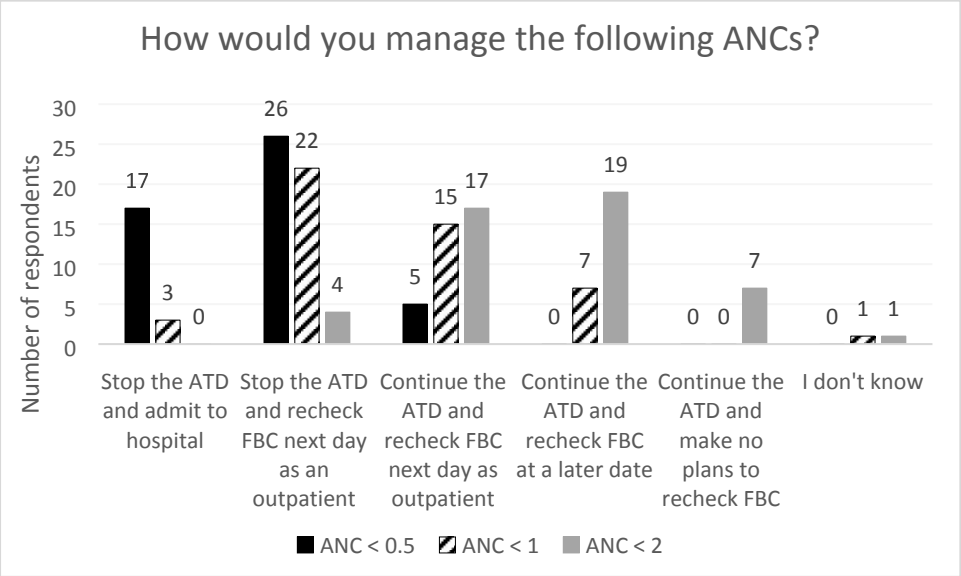
TRAbs = Thyroid Receptor Antibody Tests. ATD = Anti-Thyroid Drug

Figure 3: The measurement of FBC in relation to ATD treatment



FBC = Full Blood Count. ATD = Anti-Thyroid Drug. TFT = Thyroid Function Test

Figure 4: Actions clinicians recommend after a low ANC



ANC = Absolute Neutrophil Count. ATD = Anti-Thyroid Drug. FBC = Full Blood Count