

Data Sheets

A randomised study of two anti-thyroid drug treatment regimens in young people with thyrotoxicosis

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Study Summary

1. Diagnosis of thyrotoxicosis made at DGH or tertiary unit
2. Patient can be commenced on carbimazole 0.75mg/kg (± propranolol).
3. Explanation and information leaflet downloaded and follow-up arranged with endocrinologist in ~ 2 weeks
4. **Visit 1 (~2 weeks):** Patient / family would like to participate– Consent.
5. Patient details recorded (including thyroid function at diagnosis).
6. Baseline bloods taken and imaging arranged if not performed already (ultrasound +/- isotope study).
7. **Randomisation.** This will be undertaken at the BSPED Clinical Trials Unit located in the Department of Paediatrics, University of Cambridge. Patients will be randomised to one of two standard antithyroid treatments (block and replace or dose titration) using the minim program according to age (< or > 10 yrs), free T4 levels (≤ 50pmol/l or > 50pmol/l), gender and region. Patients will be assigned a unique study reference number.
8. Treatment – ‘Block and Replace’ regimen or ‘Dose Titration’
9. **Visit 2 – 4 weeks post diagnosis:** Bloods for central analysis (antibodies and EDTA) taken at this venepuncture if not already collected
10. Assessment at 4 weeks, 8, 12, 16, 26 weeks – follow guidelines
11. ~3 monthly review with annual assessment there-afterwards
12. Try and keep to visit schedule if at all possible.
13. Extra visits if thought to be indicated by clinician – complete ‘additional visit’ sheet (page 40/41).
14. **Annual assessment:** information as per 3 monthly review except that pubertal staging documented (end of years 1,2,3) and thyroid ultrasound and bone age required (end of year 3).
15. Treatment for 36 months then stop therapy
16. 3 monthly review with bloods off therapy
17. Outcome at 4 (and 6) years including pubertal status, thyroid U/S, bone age.
18. Patients requiring definitive therapy (radio-iodine or surgery) will be followed up with data collected as per the protocol.

Study protocol – Summary

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Investigations at diagnosis

1. Bloods (analysed locally)

- Thyroid function tests TSH, FT4, (and FT3 or total T3 if available).

2. Bloods (to be analysed centrally – these can be taken at visit 2)

- Antibodies – 2mls clotted
- Blood for genetic studies
 - patient (4mls EDTA)
 - parents (4ml EDTA)

Forward to: Children's Out Patients, Royal Victoria Infirmary,
Newcastle-upon-Tyne, NE1 4LP

3. Imaging

- Thyroid imaging – ultrasound and / or isotope scan (^{123}I or $\text{Tc}^{99\text{m}}$)
- Bone age

	Exam ⁿ	Possible side effects incl. sore throats	Thyroid function	Antibodies	Bone age	Thyroid U/S	Other
Diagnosis: 0 wks	*		*				
Visit 1 - Consent & randomisation	*	*			*	*	• Isotope scan
Visit 2: 4 wks	*	*	*	* (Analysed centrally)			• Genetic Studies (any time in the first weeks of therapy)
Visit 3: 8 wks	*	*	*				
Visit 4: 12 wks	*	*	*				
Visit 5: 16 wks	*	*	*				
Visit 6: 6 mths	*	*	*				
Visit 7: 9 mths	*	*	*				
Visit 8: :12mths	*	*	*				
Visit 9: 15 mths	*	*	*				
Visit 10:18 mths	*	*	*				
Visit 11: 21 mths	*	*	*				
Visit 12: 24 mths	*	*	*				
Visit 13: 27 mths	*	*	*				
Visit 14: 30 mths	*	*	*				
Visit 15: 33 mths	*	*	*				
Visit 16: 36 mths	*	*	*	*	*	*	
Visit 17: 39 mths	*		*				
Visit 18: 42 mths	*		*				
Visit 19: 45 mths	*		*				
Visit 20: 48 mths	*	*	*	*	*	*	

Clinicians will be contacted regarding outcome at 72 months

Baseline & Randomisation Form (Visit 1)

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **01** Week

DOB .. Date ..

Height . cm Weight kg

Pubertal status G B PH Sex M/F

Symptoms.....
.....

Biochemistry (at diagnosis)

Serum TSH mU/l Serum FT4

Serum T3 Serum FT3

Treatment

Carbimazole/PTU/Other.....

Dose

Examination

Pulse Blood pressure /

Other

Eye signs None

Signs, no symptoms
(eg retraction, stare, lid lag, mild proptosis to 22mm)

Proptosis > 22mm / Extraocular muscle involvement
Corneal involvement / visual impairment

Visit 1 and randomisation - *continued*

Possible drug side effects

Symptom

Start date

Stop date

Continuing

Yes / No

Severity mild / moderate / severe

Serious

Yes / No

Relationship to study drug

Number of occurrences

Family history.....

.....

...

Bone Age

.

Chronological Age

.

Thyroid Ultrasound

Size: Transverse diameter

Left lobe length

Right lobe length

Morphology

Nodules?

Diameter of largest nodule .cm

Other comments

Isotope scan result

Comments

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **02** Week **04**

DOB .. Date ..

Height .cm Weight kg

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

.

Possible drug side effects

Symptom

Start date Stop date Continuing Yes / No

Severity mild / moderate / severe Serious Yes / No

Relationship to study drug

Number of occurrences

Examination

Pulse Blood pressure /

Other

Eye signs None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l Serum FT4

Serum T3 Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **03** Week **08**

DOB .. Date ..

Height .cm Weight kg

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

.

Possible drug side effects

Symptom

Start date Stop date

Severity mild / moderate / severe

Relationship to study drug

Number of occurrences

Continuing Yes / No

Serious Yes / No

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l Serum FT4

Serum T3 Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **04** Week **12**

DOB .. Date ..

Height . cm Weight kg

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

Possible drug side effects

Symptom			
Start date	Stop date	Continuing	Yes / No
Severity mild / moderate / severe		Serious	Yes / No
Relationship to study drug			
Number of occurrences			

Examination

Pulse Blood pressure /

Other

Eye signs None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm)

Proptosis > 22mm / Extraocular muscle involvement
Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l Serum FT4

Serum T3 Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **05** Week **16**

DOB .. Date ..

Height . cm Weight kg

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

Possible drug side effects

Symptom			
Start date	Stop date	Continuing	Yes / No
Severity mild / moderate / severe		Serious	Yes / No
Relationship to study drug			
Number of occurrences			

Examination

Pulse Blood pressure /

Other

Eye signs None

Signs, no symptoms (eg retraction, stare, lid lag, mild proptosis to 22mm)
Proptosis > 22mm / Extraocular muscle involvement
Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l Serum FT4
Serum T3 Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **06** Week **26** (6/12)

DOB .. Date ..

Height . cm Weight kg

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

Possible drug side effects

Symptom
Start date Stop date Continuing Yes / No
Severity mild / moderate / severe Serious Yes / No
Relationship to study drug
Number of occurrences

Examination

Pulse Blood pressure /
Other

Eye signs	None	<input type="checkbox"/>
	Signs, no symptoms (eg retraction, stare, lid lag, mild proptosis to 22mm)	<input type="checkbox"/>
	Proptosis > 22mm / Extraocular muscle involvement	<input type="checkbox"/>
	Corneal involvement / visual impairment	<input type="checkbox"/>

Biochemistry

Serum TSH mU/l Serum FT4

Serum T3 Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **07** Week **39** (9/12)

DOB .. Date ..

Height . cm Weight kg

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

.

Possible drug side effects

Symptom

Start date Stop date

Severity mild / moderate / severe

Relationship to study drug

Number of occurrences

Continuing Yes / No

Serious Yes / No

Examination

Pulse

Blood pressure /

Other

Eye signs

None	<input type="checkbox"/>
Signs, no symptoms (eg retraction, stare, lid lag, mild proptosis to 22mm)	<input type="checkbox"/>
Proptosis > 22mm / Extraocular muscle involvement Corneal involvement / visual impairment	<input type="checkbox"/>

Biochemistry

Serum TSH mU/l Serum FT4

Serum T3 Serum FT3

Annual review (year 1)

**A prospective, randomised study of two antithyroid drug
treatment regimens in young people with thyrotoxicosis**

Patient Number Visit **08** Week **52**

DOB .. Date ..

Height . cm Weight kg

Pubertal status G B PH

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

.

Possible drug side effects

Symptom

Start date

Stop date

Continuing

Yes / No

Severity mild / moderate / severe

Serious

Yes / No

Relationship to study drug

Number of occurrences

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Annual review (end of year 1/2) - *continued*

Biochemistry

Serum TSH mU/l

Serum FT4

Serum T3

Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **09** Week **65**_(15/12)

DOB .. Date ..

Height .cm Weight kg

Treatment
Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

Symptoms.....

.

Possible drug side effects

Symptom

Start date

Stop date

Continuing

Yes / No

Severity mild / moderate / severe

Serious

Yes / No

Relationship to study drug

Number of occurrences

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l

Serum FT4

Serum T3

Serum FT3

Annual review (year 2)

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **12** Week **104**

DOB . .

Date . .

Height . cm

Weight kg

Pubertal status G B PH

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **13** Week **17** (27/12)

DOB ..

Date ..

Height .cm

Weight kg

Treatment

Carbimazole/PTU

Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

Possible drug side effects

Symptom

Start date Stop date Continuing Yes / No

Severity mild / moderate / severe Serious Yes / No

Relationship to study drug

Number of occurrences

Examination

Pulse

Blood pressure /

Other

Eye signs None
Signs, no symptoms
(eg retraction, stare, lid lag, mild proptosis to 22mm
Proptosis > 22mm / Extraocular muscle involvement
Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l Serum FT4

Serum T3 Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **14** Week **130**_(30/12)

DOB .. Date ..

Height .cm Weight kg

Treatment

Carbimazole/PTU Dose

Pubertal status G B PH

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

.

Possible drug side effects

Symptom

Start date Stop date Continuing Yes / No

Severity mild / moderate / severe Serious Yes / No

Relationship to study drug

Number of occurrences

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Annual review (end of year 3) - *continued*

Biochemistry

Serum TSH mU/l

Serum FT4

Serum T3

Serum FT3

Bone Age .

Chronological Age .

Thyroid Ultrasound

Size: Transverse diameter
 Left lobe length
 Right lobe length

Morphology

Nodules?

Diameter of largest nodule . cm

Other comments

General comments

**A prospective, randomised study of two antithyroid drug
treatment regimens in young people with thyrotoxicosis**

Patient Number Visit **17** Week **169**_(39/12)

DOB . . Date . .

Height . cm

Weight kg

Symptoms.....

.

Treatment ?

.....

.....

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l

Serum FT4

Serum T3

Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **18** Week **182**_(42/12)

DOB ..

Date ..

Height .cm

Weight kg

Symptoms.....

.

Treatment ?

.....

.....

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l

Serum FT4

Serum T3

Serum FT3

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Patient Number Visit **19** Week **195** (45/12)

DOB ..

Date ..

Height . cm

Weight kg

Symptoms.....

.

Treatment ?

.....

.....

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l

Serum FT4

Serum T3

Serum FT3

Final visit (end of year 4)

**A prospective, randomised study of two antithyroid drug
treatment regimens in young people with thyrotoxicosis**

Patient Number Visit **20** Week **208**

DOB .. Date ..

Height .cm Weight kg

Pubertal status G B PH

Symptoms.....

.

Treatment ?

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Possible drug side effects

Symptom

Start date Stop date

Severity mild / moderate / severe

Relationship to study drug

Number of occurrences

Continuing

Serious

Yes / No

Yes / No

Definitive therapy ?

Radio-iodine ?

If so when and dose

Surgery ?

If so when

Final visit (end of year 4) - *continued*

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l

Serum FT4

Serum T3

Serum FT3

Bone Age .

Chronological Age .

Thyroid Ultrasound

Size: Transverse diameter
Left lobe length
Right lobe length

Morphology

Nodules?

Diameter of largest nodule . cm

Other comments

General comments

A prospective, randomised study of two antithyroid drug treatment regimens in young people with thyrotoxicosis

Extra Visit

Patient Number

Week

DOB ..

Date ..

Height . cm

Weight kg

Treatment

Carbimazole/PTU Dose

Thyroxine +/- Dose

Other.....

Symptoms.....

.

Reason for extra visit.....

.....

.....

...

Possible drug side effects

Symptom

Start date Stop date

Severity mild / moderate / severe

Relationship to study drug

Number of occurrences

Continuing Yes / No

Serious Yes / No

Examination

Pulse

Blood pressure /

Other

Eye signs

None

Signs, no symptoms

(eg retraction, stare, lid lag, mild proptosis to 22mm

Proptosis > 22mm / Extraocular muscle involvement

Corneal involvement / visual impairment

Biochemistry

Serum TSH mU/l Serum FT4

Serum T3 Serum FT3

Other comments

Data sheet handling

The data sheets should be photocopied. The original should be then be sent to the CTU in Cambridge whilst the photocopy should be inserted in the patients' notes

Appendix (i)

Adverse event reporting – thyrotoxicosis study

MREC Ref No: 04/12/015

Information regarding adverse events will be forwarded to, and reviewed by the Principal investigator. Investigators will also be expected to abide by the standard 'Yellow Card' reporting system.

Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product

Adverse reaction of an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship

Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

Serious adverse event or serious adverse reaction

Any untoward medical occurrence or effect that:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Expected adverse drug reactions

In order to minimise unnecessary work, it is recommended that all expected adverse drug reactions and all expected serious adverse events are listed in the protocol (otherwise they will have to be reported as SUSARs).

Sometimes, unexpected adverse drug reactions and unexpected serious adverse events become 'expected' during the trial, in which case the protocol² should be amended and such events would not need reporting. The Sponsor and Chief Investigator and Data Monitoring Committee, if applicable, should determine whether any events become 'expected' during the course of the trial and apply for MHRA and Ethics Committee approval for a substantial amendment.

Expected Serious Adverse Events

In order to minimise unnecessary work, it is recommended that all expected adverse drug reactions and all expected serious adverse events are listed in the protocol (otherwise they will have to be reported as SUSARs).

Recording and evaluation of adverse events

Individual adverse events should be evaluated by the investigator and, where indicated, they should be reported to the sponsor for evaluation. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

The sponsor has to keep detailed records of all AEs reported to him by the investigator(s) and to perform an evaluation with respect to seriousness, causality and expectedness.

Assessment of seriousness

- Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated
- Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
- Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the subject's life is at risk from the event.

Assessment of causality

- Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

Anti-thyroid drugs. Expected adverse events

1a Carbimazole - Expected adverse drug reactions

Nausea,
Mild Gastro-intestinal disturbance
Headache
Rashes and pruritis
Arthralgia

1b Carbimazole- Expected serious adverse events

Bone marrow suppression including:
leucopenia,
neutropenia,
pancytopenia,
agranulocytosis

2a Propylthiouracil - Expected adverse drug reactions

Nausea, mild Gastro-intestinal disturbance
Headache
Rashes and pruritis
Arthralgia

2b Propylthiouracil - Expected serious adverse events

Vasculitis
Hepatitis
Hepatic necrosis
Encephalopathy
Lupus erythematous-like syndrome
Bone marrow suppression including neutropenia pancytopenia,
agranulocytosis

Adverse events

Patient ID:

Visit date (dd-mm-yy)

Evaluating physician name

Onset of adverse event (dd-mm-yy)

Adverse event description
(Please record symptoms in order of seriousness)

If other, please specify

Was the event serious (tick) YES NO

If YES, please specify

Outcome of the adverse event

Date of outcome (dd-mm-yy)

Causality related to ATD, assessed by physician

Name of suspected ATD medication

Dose of ATD mg Equivalent to mg/kg/day

Changes of ATD medication

Has the adverse event been reported to the local health authorities? YES NO

If YES, please state by whom:

Concomitant medication	
Name of medication	Date
<input type="text"/>	<input type="text"/>

Date: _____ (Signed) _____ (missing data = NA)