

PROPYLTHIOURACIL



“The Pale Blue Dot”, (detail) Earth from 6 billion kms, suspended in the infinite abyss of space, as seen from Voyager I, (February 14, 1990, NASA).

*...look down once more and see how many heavens
I have already set beneath your feet...”*

*With my eyes I returned through every one
of the seven spheres below, and saw this globe of ours
to be such that I smiled, so small and mean did it appear.*

*That opinion which judges it as least
I now approve as best, and those whose thoughts
are fixed on other things may truly be called just...*

*All seven planets were revealed
their sizes, their velocities,
and how distant from each other their abodes*

*The earth, that little threshing ground that makes men so fierce and mad,
from hills to rivermouths, I saw it all
while I was being wheeled with the eternal Twins.
Then I turned my eyes once more to those fair eyes.*

*Dante Alighieri, Paradiso XXII, 128 - 154,
The Divine Comedy, (1306-1317)*

From this distant vantage point, the Earth might not seem of any particular interest. But for us, it's different. Consider again that dot. That's here. That's home. That's us.

On it everyone you love, everyone you know, everyone you ever heard of, every human being who ever was, lived out their lives.

The aggregate of our joy and suffering, thousands of confident religions, ideologies, and economic doctrines, every hunter and forager, every hero and coward, every creator and destroyer of civilization, every king and peasant, every young couple in love, every mother and father, hopeful child, inventor and explorer, every teacher of morals, every corrupt politician, every "superstar", every "supreme leader", every saint and sinner in the history of our species lived there - on a mote of dust suspended in a sunbeam.

The Earth is a very small stage in a vast cosmic arena.

Think of the rivers of blood spilled by all those generals and emperors so that in glory and triumph they could become the momentary masters of a fraction of a dot. Think of the endless cruelties visited by the inhabitants of one corner of the dot on scarcely distinguishable inhabitants of some other corner of the dot. How frequent their misunderstandings, how eager they are to kill one another, how fervent their hatreds. Our posturings, our imagined self-importance, the delusion that we have some privileged position in the universe, are challenged by this point of pale light.

Our planet is a lonely speck in the great enveloping cosmic dark. In our obscurity - in all this vastness - there is no hint that help will come from elsewhere to save us from ourselves.

The Earth is the only world known, so far, to harbor life.

There is nowhere else, at least in the near future, to which our species could migrate. Visit, yes. Settle, not yet. Like it or not, for the moment, the Earth is where we make our stand. It has been said that astronomy is a humbling and character building experience. There is

perhaps no better demonstration of the folly of human conceits than this distant image of our tiny world.

To me, it underscores our responsibility to deal more kindly with one another and to preserve and cherish the pale blue dot, the only home we've ever known.

Carl Sagan, speech given at Cornell University, October 13, 1994

Dante, having been guided by the shade of the Roman poet Virgil through the horrific Circles of Hell and the terrifying Terraces of Purgatory, finally gets to ascend the Nine Celestial Spheres of the Heavens. In this place his guide is Beatrice, the woman he loved from afar on Earth, but tragically died at a very young age. From the seventh celestial sphere of Saturn, Beatrice elevates Dante into the eighth sphere, that of the Fixed Stars, within whose realm he is carried along by his natal sign, the "eternal twins", the great Constellation of Gemini. Dante looks down through the eight crystalline spheres of the planets below him, and is awestruck by what he sees. Finally he appreciates the grand scheme of the Universe. The Earth itself seems so tiny and insignificant that he cannot help but smile. He sees the "tiny threshing ground" upon which the masses of humanity live out their short and miserable lives in conflict, jealousy, prejudice and hatred. Beatrice shows him a grander and incomprehensibly wondrous vision of the true nature of the Universe.

In the early Fourteenth century, Dante Alighieri gave humanity its first vision of the totality of the Ptolemaic vision of our Solar System, as it was then understood, and although only within the imagination it truly struck an immensely powerful cord in the medieval mind. Then almost seven centuries later, on the back of the Renaissance, the great Enlightenment and the dawn of the Space Age, another magisterial "natural philosopher" by the name of Carl Sagan unveiled to the world on October 13, 1994, a true and actual vision of our Solar System. As the deep space probe Voyager I, was about to depart the Solar System, Sagan had convinced NASA authorities to take the opportunity to take one last photograph. The craft should be turned momentarily back toward the Earth - from the vantage point of over 6 billion kilometers, humanity had a unique opportunity to actually see what Dante could only imagine. Though the Ptolemaic system of the Solar System had long been discredited, Carl Sagan's message to the world nonetheless would parallel exactly the sentiments of one of the greatest literary geniuses to have ever lived. The message he imparted was that we are an incomprehensibly insignificant part of the cosmos, and - for the foreseeable future - the tiny fragile speck of dust we live on will be our only home - indeed perhaps the only place of life in the Universe. We live in a new golden age of Astronomy, one that Carl Sagan introduced to the popular mind. His conclusion was clear - we must see and understand the bigger picture of our existence and abandon our pitiful and self-destructive "threshing floor" mentality for pursuits of far grander and more noble designs.

The anti-thyroid agent carbimazole is recommended as the preferred agent in cases of hyperthyroidism, yet we must, as Carl Sagan and Dante Alighieri urged, always keep an open mind for the bigger picture! In prescribing carbimazole there are three situations in which a bigger picture must be considered - the first trimester of pregnancy, when significant allergy exists and the thyroid storm. In these particular situations the agent propylthiouracil becomes the preferred anti-thyroid drug.

PROPYLTHIOURACIL

Introduction

Propylthiouracil, (“PTU”) is an anti-thyroid agent.

Carbimazole is the recommended initial first line treatment for **mild** to **moderate** hyperthyroidism.

Propylthiouracil is only indicated for:

1. Maintenance therapy in the first trimester of pregnancy.
2. Patients who have experienced adverse events with carbimazole.
3. Thyroid storm:
 - PTU has some theoretical advantages in thyroid storm, as it not only inhibits thyroid hormone synthesis but also inhibits the peripheral conversion of T4 to T3. It also has the most rapid effect (within 1 hour) ¹

Despite safety concerns in long term management of hyperthyroidism, propylthiouracil is preferred to carbimazole in the treatment of thyroid storm. This is due to the additional peripheral blocking of conversion of T4 to T3 with high-dose propylthiouracil. ¹

Propylthiouracil is on the World Health Organization’s List of Essential Medicines, the most effective and safe medicines needed in a health system

History

The two most important anti-thyroid drugs were discovered in the early 1940s.

These were the prototype **propylthiouracil (PTU)** and **sulfaguanidine**, from which **methimazole** and **carbimazole** were developed.

Propylthiouracil was approved by the US Food and Drug Administration in 1947.

Chemistry

The major antithyroid drugs are relatively simple molecules known as thionamides, which contain a sulfhydryl group and a thiourea moiety within a heterocyclic structure.

Propylthiouracil is a thioamide derivative.

Classification

The principle anti-thyroid drugs fall into 2 groups:

1. **Thiouracils:**
 - Propylthiouracil
2. **Sulphur-containing imidazole derivatives:**
 - Carbimazole
 - Methimazole

Preparations

Propylthiouracil as:

Tablets:

- 50 mg

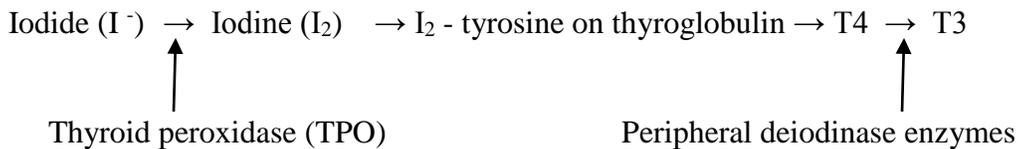
Mechanism of Action

Propylthiouracil has two main mechanisms of action:

1. As for carbimazole it prevents the **thyroid peroxidase** enzyme from iodinating tyrosine molecules on thyroglobulin, hence reducing the production of the thyroid hormones T3 (tri-iodothyronine) and T4 (thyroxine).

Thyroid peroxidase oxidizes **iodide ions** to form **iodine atoms** for addition onto tyrosine residues on thyroglobulin for the production of T4 and T3.

T3 is the more metabolically active hormone produced from T4. T4 is deiodinated by three deiodinase enzymes to produce the more active triiodothyronine.



Carbimazole does not affect the uptake of iodine by the thyroid gland (which propylthiouracil may) and this is important in the concomitant treatment of thyrotoxicosis with radioactive iodine.

2. Propylthiouracil *also* inhibits *peripheral* conversion of T4 to the more active T3.

Pharmacodynamics

Propylthiouracil has the most rapid onset of effect (within 1 hour) of the 3 main anti-thyroid medications currently in use.

This pharmacodynamic property makes it a suitable agent for the treatment of **thyroid storm**.

The long duration of action of **methimazole** allows once-daily dosing, whereas **propylthiouracil** is usually given two or three times per day.

Although propylthiouracil is used for the total treatment of hyperthyroidism, the duration of treatment necessary to produce a prolonged remission varies from 6 months to several years, with an average duration of one year.

Pharmacokinetics

Absorption:

- Propylthiouracil is rapidly absorbed from the GIT.
Peak levels are reached within 2 hours, however blood levels do not closely correlate with clinical effect.

Distribution

- Protein binding is around 80%, mainly to albumin.
- Propylthiouracil can cross the human placenta
- Propylthiouracil is excreted into breast milk.

Metabolism and excretion:

- Propylthiouracil is metabolised in the liver and is excreted in the bile (primary route) with approximately 30% being excreted in the urine as metabolites or whole drug.

Indications

Carbimazole is the recommended **initial first line** treatment for mild to moderate hyperthyroidism, including for:

1. Graves' disease
2. Short-term treatment before thyroid surgery, or before and after radioactive iodine treatment.

Propylthiouracil is only indicated for:

1. Maintenance therapy in the first trimester of pregnancy.
2. Patients who have experienced adverse events with carbimazole.

3. Thyroid storm:

- PTU has some theoretical advantages in thyroid storm, as it not only inhibits thyroid hormone synthesis but also inhibits the peripheral conversion of T4 to T3. It also has the most rapid effect (within 1 hour) ¹

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Contra-indications/precautions

These include:

1. Known hypersensitivity
2. Previous agranulocytosis with an antithyroid drug (contraindicated).
3. Pregnancy
 - Propylthiouracil is generally preferred in first trimester; carbimazole is preferred after this time (see below)

Pregnancy

Propylthiouracil is a category C drug with respect to pregnancy

Category C drug are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

A single case series has reported possible propylthiouracil (PTU) associated birth defects, including face and neck and urinary tract malformations, however, it is usually less severe than the defects observed following carbimazole exposure.

PTU is recommended as the treatment of choice for hyperthyroidism in the **first trimester** of pregnancy and in cases of drug allergy to carbimazole.

After the first trimester, PTU should be changed to **carbimazole** due to concerns of hepatotoxicity.

Additionally, a single case of PTU-induced agranulocytosis in pregnancy has also been reported following use of the medicine in the third trimester.

If PTU is used during pregnancy, follow-up and monitoring of both maternal and fetal wellbeing including maternal complete blood counts, liver function and thyroid function tests (include TSH and FT4) are recommended.

Breast feeding

Small amounts of propylthiouracil (PTU) are excreted in human breast milk, but adverse effects have not been noted in breastfed infants.

As PTU may potentially cause hepatotoxicity in both mother and breastfed infant, carbimazole is the medicine of choice during breastfeeding.

However, if PTU is the treatment of choice, use the minimum effective daily dose and observe the breastfed infant for adverse effects such as skin rashes, vomiting and signs of infection.

Consider monitoring thyroid function and full blood counts of the breastfed infant periodically.

Adverse Effects

As a class adverse effects of the anti-thyroid drugs usually occur during the first 8 weeks of treatment.

These can include:

1. Pruritis / mild rashes:

- Itching and mild rashes may respond to antihistamines while continuing treatment.

If a change in treatment is needed, the 2 drugs can often be interchanged without recurrence of adverse effects (unless agranulocytosis occurred, in which case seek specialist advice for future management).

2. GIT upset:

- Nausea, vomiting abdominal cramps.

3. Blood dyscrasias:

- Agranulocytosis is the most serious adverse effect.

Agranulocytosis is thought to be autoimmune mediated, and antigranulocyte antibodies have been demonstrated by immunofluorescence studies and cytotoxicity assays.

It is most likely in first 3 months of treatment and then the risk declines.

It can have a *rapid* onset.

4. Hepatotoxicity:

- Asymptomatic increases in serum aminotransferases commonly occur during the first 2 months of **propylthiouracil** treatment, but usually resolve with continued treatment.

Serious hepatotoxic reactions (usually hepatocellular hepatitis) occur rarely with propylthiouracil and may be immune-based.

Cholestatic jaundice has rarely been associated with **carbimazole**.

As the mechanisms of hepatic damage with the 2 drugs are thought to be different, the other drug may be tried cautiously in cases of drug-induced hepatic adverse effects.

Dosing

Usual adult dosing is:

Hyperthyroidism

Oral, initially 200 - 400 mg daily in 2 - 4 doses for 3 - 4 weeks.

Adjusted regimen, maintenance dose 25 - 300 mg daily in divided doses, according to response.

Dosage should be titrated against thyroid function until the patient is euthyroid in order to reduce the risk of overtreatment with resultant hypothyroidism.

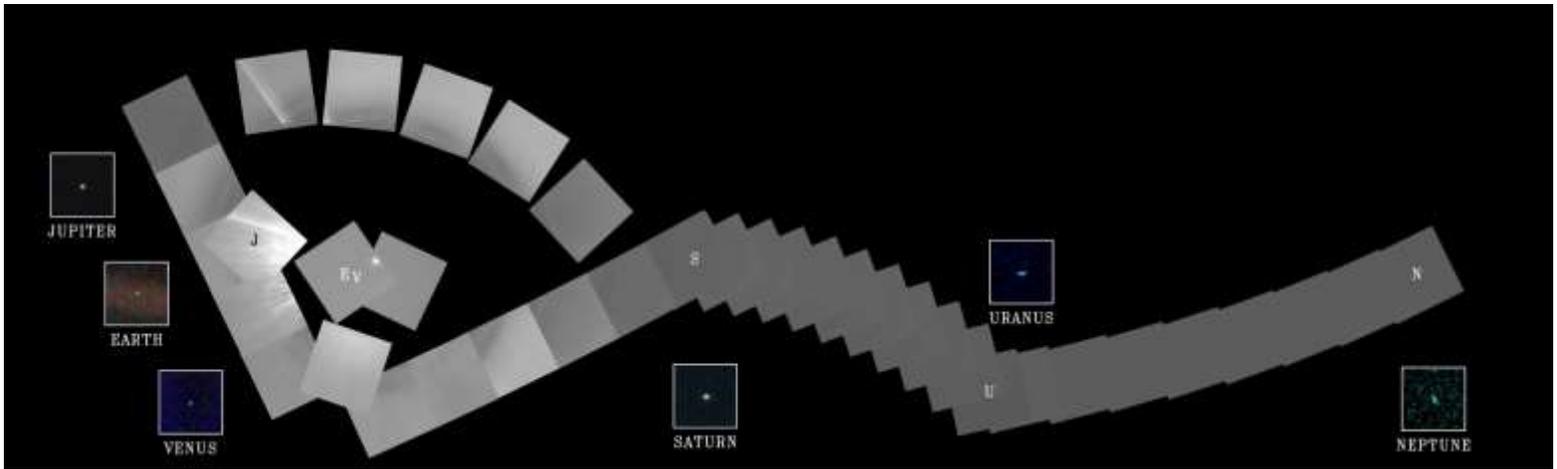
Thyroid storm:

Oral 600 - 1200 mg daily, in divided doses, gradually reduced.

Monitoring:

All patients receiving propylthiouracil should have close monitoring of:

- FBE
- LFTs
- TFTs



*The first, and only image we have, of the planets of our Sun's family, the Solar System,
(Voyager I, February 14, 1990, NASA).*

*....All seven planets were revealed
their sizes, their velocities,
and how distant from each other their abodes*

*The earth, that little threshing ground that makes men so fierce and mad,
from hills to rivermouths, I saw it all....*

*Dante Alighieri, Paradiso XXII, 128 - 154,
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