## Propylthiouracil and Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis

### Introduction

Propylthiouracil (PTU) is an antithyroid agent and is indicated for treatment of *hyperthyroidism* [1, 2]. It is pharmacologic categorised within the group thionamide or thioamide derivates, together with carbimazole and its metabolite methimazole. Propylthiouracil has been marketed internationally since 1948 [2].

Propylthiouracil inhibits the synthesis of thyroid hormones through several ways: interference with the incorporation of iodine into the tyrosyl residues thyroglobulin and inhibition of coupling of the idiotyrosyl residues to form triiodothyronine (T3) and thyroxine (T4) by inhibition of thyroid peroxidase. It also inhibits conversion of T4 to T3 in peripheral tissues [1, 3].

Vasculitis is a group of autoimmune diseases characterised by inflammation of the vessel walls.
The affected vessel size, type and location determines the specific type of vasculitis. Vasculitis can occur as a primary process or secondary to another underlying disease [4]. One of the various forms of vasculitis is Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which is characterized by the presence of ANCAs [5, 6]. ANCAs are autoantibodies directed against enzymes in the granules of polynuclear neutrophils and monocytes. ANCAs are mostly directed against the enzymes protein kinase 3 (PR3) or myeloperoxidase (MPO) [7]. PR3 localizes in the cytoplasm while MPO surrounds the nucleus. An indirect immunofluorescence (IFF) test is used to determine which ANCAs are present, highlighting either the cytoplasmatic ANCA (c-ANCA) which is associated with granulomatosis with polyangiitis (PGA or Churg Strauss Syndrome) and microscopic polyangiitis (MPA) or the perinuclear ANCA (p-ANCA) associated with eosinophilic granulomatosis with polyangiitis (EGPA or Wegener's disease) [7]. ANCAs are also associated with other autoimmune diseases such as rheumatoid arthritis [8], which cannot be distinguished from this IFF test. An additional enzyme linked immunosorbent assay (ELISA) is therefore required to confirm the indication. AAV affects the small and medium vessels, potentially causing damage to several organs [9, 10].

### Reports

In the period from July 8, 2000 until July 27, 2022 the Netherlands Pharmacovigilance Centre Lareb received 7 reports on propylthiouracil and vasculitis. The reports are listed in Table 1.

Table 1. Reports of vasculitis associated with propylthiouracil in the Lareb database

| No | ID, sex, age, primary source | Drug, Dosage | Indication | Concomitant medication | Reported ADRs | Latency after start | Action taken | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | NL-LRB-00797106, male, 70 years and older, Physician | Propylthiouracil Tablet 50Mg, 150 milligram / 1 Days | Hyperthyroidism | Valsartan Tablet 80Mg, Tiotropium/ Olodaterol nebulizer solution 2,5/2,5Ug/Do, Unspecified NSAID | Anti neutrophil cytoplasmic antibody positive vasculitis, Haemoptysis, Acute kidney injury | 2 Years<br>---<br>2 Years<br>---<br>2 Years | Drug Withdrawn | Fatal,<br>Fatal,<br>Fatal |
| 2 | NL-AUROBINDO-AUR-APL-2020-047094, female, 30-40 Years, Other health professional | Propylthiouracil | Hyperthyroidism | | Arthralgia, Knee effusion, Myalgia, Stiffness, Vasculitis | - | Drug Withdrawn | Recovered,<br>Recovered,<br>Recovered,<br>Recovered,<br>Recovered |
| 3 | NL-AUROBINDO-AUR-APL-2020-047093, female, 70 Years and older, Other health professional | Propylthiouracil | Hyperthyroidism | | Erysipelas, Erythema, Fever, Knee pain, Vasculitis | 6 Years<br>---<br>6 Years<br>---<br>6 Years<br>---<br>6 Years<br>---<br>6 Years | Drug Withdrawn | Recovered,<br>Recovered,<br>Recovered,<br>Recovered,<br>Recovered |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 4 | NL-AUROBINDO-AUR-APL-2020-047097, female, 40-50 Years, Other health professional | Propylthiouracil | Hyper-thyroidism | Iodine | General malaise, Relapsing fever, Wegener's granulomatosis, Weight loss | 6 Years<br>---<br>6 Years<br>---<br>6 Years<br>---<br>6 Years | Drug Withdrawn | Recovered, Recovered, Recovered, Recovered |
| 5 | NL-AUROBINDO-AUR-APL-2020-047092, female, 30-40 Years, Other health professional | Propylthiouracil | Hyper-thyroidism | | Conjunctivitis, Fever, Painful joints, Scleritis, Sore throat, Vasculitis, Palatal ulcer | - | Drug Withdrawn | Recovered, Recovered, Recovered, Recovered, Recovered, Recovered, Recovered |
| 6 | NL-LRB-48404, female, 40-50 Years, Physician | Propylthiouracil um Tablet 50Mg, 300 milligram / 1 Days | Hyper-thyroidism | Sotalol Tablet 80Mg, Non Specified Drug, Levothyroxine Tablet 25Ug | Fatigue, Pruritus, Abdominal pain, Vasculitis cerebral | 5 Months<br>---<br>5 Months<br>---<br>5 Months<br>---<br>5 Months | Drug Withdrawn | Not Recovered, Not Recovered, Not Recovered, Not Recovered |
| 7 | NL-LRB-28865, female, 30-40 Years, Physician | Propylthiouracil um Tablet 50Mg, 3 dosage form / 1 Days | Thyro-toxicosis | Clarithromycin Tablet 250Mg | Vasculitis, Agranulocytosis | 23 Days<br>---<br>22 Days | Drug Withdrawn | |

Additional information on the cases:
Cases 2, 3, 4 and 5 were reported based on a case series in the literature [11].
1. Anti-MPO positive. Patient was treated with methylprednisolone and rituximab. Reported cause of death: ANCA-positive vasculitis with respiratory insufficiency. In this report concomitant use of valsartan and an unspecified NSAID has been mentioned, which both could cause vasculitis [12-15].
2. Arthralgia developed 1 month after start PTU. Tests for extractable nuclear antigens (ENA), anti-perinuclear factor (APF) and rheumatoid factor were positive. Patient was treated with a NSAID for 2 years. After withdrawal of this treatment, arthralgia reappeared, together with myalgia, morning stiffness and knee hydrops. ENA, APF and rheumatoid factor were negative, ANCA-positive. Within 6 weeks after withdrawal of PTU, the symptoms disappeared and the ANCA titre decreased.
3. Skin biopsy: necrotizing vasculitis. ANCA-positive, with P-ANCA pattern. After withdrawal of PTU, the patient improved greatly and the ANCA titre decreased.
4. History of chronic leucopenia. Urinalysis: microscopic haematuria. CT-abdomen: enlarged spleen. ANCA-positive, with P-ANCA pattern. PTU was withdrawn and the patient was subsequently treated with 131-I. 5 Months later the symptoms were unchanged. Wegener's granulomatosis was suspected. After treatment with prednisone and cyclophosphamide the symptoms resolved completely.
5. Patient was treated with PTU for 2 years and thereafter withdrawn. PTU treatment had to be resumed after 1 year because of hyperthyroidism relapse. 4 Months later, the patient developed the reported symptoms. Serum erythrocyte sedimentation rate: high. Chest radiograph: hilar lymphadenopathy, and enlarged spleen. ANCA-positive, with P-ANCA pattern. Anti-PIO and anti-HNE positive. Within 4 weeks after PTU withdrawal, the patient's condition improved greatly. Anti-HNE disappeared and anti-PR3 persisted for a year.
6. PTU was withdrawn and the patient was treated with prednisone and cyclophosphamide. 3 Months later, patient was not yet recovered.
7. Skin lesions mainly on lower legs. ANCA-positive, PR3-positive. EA-IgG positive and EBNA-IgG positive, which suggests an Epstein Barr virus infection the last year. Skin biopsy: thrombotic microangiopathy. Fast improvement of skin lesions after PTU withdrawal.

## Other sources of information

*SmPC*

The Dutch Summary of Product Characteristics (SmPC) of propylthiouracil does not mention vasculitis as a possible adverse drug reaction. Also, the SmPC does not warn for vasculitis nor symptoms that could be caused by vasculitis [1].

The US SmPC of propylthiouracil mentions in section 'Adverse reactions': "There are reports of a vasculitis associated with the presence of anti-neutrophilic cytoplasmic antibodies (ANCA), resulting in severe complications and death." In the section 'Warnings' it states: "Cases of vasculitis resulting in severe complications and death have been reported in patients receiving propylthiouracil therapy. The cases of vasculitis include: glomerulonephritis, leukocytoclastic cutaneous vasculitis, alveolar/pulmonary hemorrhage, cerebral angiitis, and ischemic colitis. Most cases were associated with anti-neutrophilic cytoplasmic antibodies (ANCA)-positive vasculitis. In some cases, vasculitis

resolved/improved with drug discontinuation; however, more severe cases required treatment with additional measures including corticosteroids, immunosuppressant therapy, and plasmapheresis. If vasculitis is suspected, discontinue therapy and initiate appropriate intervention."[16].

The UK SmPC of propylthiouracil mentions in section 4.8 'Undesirable effects' that vasculitis and lupus erythematosus-like syndromes have occurred in some patients taking thiourea antithyroid drugs. It also mentions cutaneous vasculitis as an adverse drug reaction [3].

*Literature*

A review article by Weng and Liu (2019) describes that in recent years, more and more drugs have been associated with drug-induced vasculitis (DIV). A large proportion of patients with DIV are characterized by ANCA positivity. The drugs associated with drug-induced ANCA-positive vasculitis are almost from all pharmacologic categories. Anti-thyroid drugs, especially PTU, and tumor necrosis factor inhibitors are most associated with DIV [9, 10]. There is no clear epidemiological data about the incidence of drug-induced AAV [9]. Balavoine et al. describe in their review article that the prevalence of ANCA-positive cases caused by PTU varied between 4 and 64%, with a median of 30%. Only 15% of ANCA-positive patients treated with anti-thyroid drugs exhibited clinical evidence of vasculitis [10]. A recent article based on ADR reports from the World Health Organization pharmacovigilance database (VigiBase) showed a median onset of drug-induced AAV (including propylthiouracil) of 9 months [17]. Several studies showed that ANCA positivity is related to the duration of antithyroid drug therapy [9, 10]. Stopping the offending drug in time may be sufficient for patients with mild symptoms. In patients with vital organs involvement, immunosuppressant therapy may be necessary to prevent further disease progression [9].

*Other databases*

On July 27th 2022 the Eudravigilance database of the European Medicines Agency contained 42 reports* of vasculitis and 47 reports* of anti-neutrophil cytoplasmic antibody positive vasculitis associated with propylthiouracil. Table 2 shows the number of the reported cases for the specific MedDRA terms. Table 2 also shows the number of the reported cases in the WHO database of the Uppsala Monitoring Centre on July 27th 2022.

Table 2. Reports of vasculitis associated with the use of propylthiouracil (PTU) in the Lareb, WHO and Eudravigilance database* (only shown when 3 reports or more were available).

| Database | Drug | ADR# | Number of reports | ROR (95% CI) |
|---|---|---|---|---|
| Lareb | PTU | Vasculitis | 4 | 110.2 (40.0 - 303.4) |
| Eudravigilance | PTU | Anti-neutrophil cytoplasmic antibody positive vasculitis | 46* | 771.3 (567.8 – 1047.7) |
| | | Vasculitis | 37* | 39.1 (28.1 – 54.2) |
| | | Cutaneous vasculitis | 6 | 12.8 (5.7 – 28.5) |
| | | Vasculitis necrotising | 5 | 94.1 (38.9 – 227.5) |
| | | Cryoglobulinaemia | 5 | 140.8 ( 58.1 – 341.3) |
| | | Diffuse vasculitis | 4 | 512.8 (187.0 – 1405.9) |
| | | Hypersensitivity vasculitis | 4 | 32.4 (12.1 – 86.6) |
| | | Henoch-Schonlein purpura | 4 | 15.6 (5.8 – 41.6) |
| | | Central nervous system vasculitis | 3 | 57.5 (18.5 – 179.2) |
| WHO | PTU | Anti-neutrophil cytoplasmic antibody positive vasculitis | 137 | 734.8 (614.1 – 879.2) |
| | | Vasculitis | 113 | 36.7 (30.4 – 44.2) |
| | | Cutaneous vasculitis | 9 | 9.5 (4.9 – 18.2) |
| | | Microscopic polyangiitis | 8 | 219.6 (108.4 – 445.1) |
| | | Hypersensitivity vasculitis | 8 | 18.5 (9.2 – 37.0) |
| | | Vasculitis necrotising | 7 | 71.7 (34.0 – 151.2) |
| | | Granulomatosis with polyangiitis | 6 | 40.8 (18.3 – 91.2) |
| | | Diffuse vasculitis | 4 | 247.5 (91.0 – 673.4) |
| | | Central nervous system vasculitis | 4 | 37.4 (14.0 – 100.0) |
| | | Henoch-Schonlein purpura | 4 | 5.0 (1.9 – 13.2) |
| | | Pulmonary vasculitis | 3 | 52.1 (16.7 – 162.3) |
| | | Eosinophilic granulomatosis with polyangiitis | 3 | 12.6 (4.1 – 39.3) |

*Searched for multiaxial High Level Term (HLT) Vasculitides and multiaxial HLT Vasculitides NEC. There was an inexplicable discrepancy between the number of the cases found in the Eudravigilance database and the number of the cases reported in the ROR calculated by Eudravigilance.

#MedDRA Preferred Term (PT). One report can contain multiples PT's.

For illustration, two cases of the Eudravigilance database are highlighted:

Case 20: A female patient of unknown age has been on continuous treatment with propylthiouracil for toxic thyroid adenoma. Approximately 4 years after start, anemia and liver cirrhosis were diagnosed (at that time of unexplained etiology). Five years later, the patient has suffered from frequent recurrent pneumonia which, at the time of this report, was determined as an anti-neutrophil cytoplasmic antibody positive vasculitis (cutaneous and pulmonary form) with diffuse alveolar haemorrhage. Lung biopsy was performed and pathohistological finding showed histological features for a drug-induced toxic effect on the lung parenchyma. It is assumed that all these medical conditions (liver cirrhosis, anti-neutrophil cytoplasmic antibody positive vasculitis and alveolar haemorrhage) are side effects of propylthiouracil. The suspected drug was discontinued and the patient was treated with corticosteroids. At the time of reporting, the patient was recovering.

Case 43: A 40-50 years old female patient was submitted to an intensive care unit in a life-threatening condition of acute renal and hepatic failure, pulmonary embolism and anemia. The patient received propylthiouracil for Basedow's disease for several years. ANCA test was p-ANCA positive, the anti-MPO test was 79 U/mL and renal biopsy confirmed anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The reporter assessed causality of the event as linked to propylthiouracil administration over a prolonged period. Propylthiouracil was reduced. The outcome of the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis was recovered with sequelae.

In the WHO database, we also searched for MedDRA High Level Terms (HLTs) Vasculitides and Vasculitides NEC associated with propylthiouracil. Most reported Preferred Terms were 'Anti-neutrophil cytoplasmic antibody positive vasculitis' (137 times) and 'Vasculitis' (113 times) in 249 unique cases. These cases concerned 210 (84.3%) females and 34 males (13.7%). In 5 reports (2.0%), the patient sex was unknown. Co-suspected or interacting drug was reported in several cases: thiamazole in 17 reports (6.8%), carbimazole in 4 reports (1.6%) and levothyroxine in 3 reports (1.2%). To date, vasculitis is no known adverse drug reaction for these drugs [2]. Most co-reported Preferred Terms were arthralgia (5.2%), antineutrophil cytoplasmic antibody positive (4.8%), pyrexia (3.8%), glomerulonephritis (3.2%), pulmonary alveolar hemorrhage (3.2%) and rash (3.2%). In 6 cases (2.4%) the outcome was reported as fatal.

*Prescription data*

Table 3. Number of patients using propylthiouracil (H03BA02) in the Netherlands [18].

| ATC-code | Drug | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|---|
| H03BA02 | Propylthiouracil | 2,121 | 2,146 | 2,113 | 2,111 | 2,048 |

*Mechanism*

In pathogenesis, primary ANCA-associated vasculitis and drug-induced ANCA-associated vasculitis share a partial pathway [9]. The exact mechanism by which drugs can induce ANCA-associated vasculitis is poorly understood and it might be multifactorial. It may involve conversion of PTU and its metabolites into cytotoxic products by myeloperoxidase. This results in a T cell and in turn B cell immunogenetic response, producing ANCA. Further, PTU metabolites may accumulate within neutrophils, bind to MPO and modify its configuration, thereby creating an autoimmune response. Another possibility is that drug-induced neutrophil apoptosis can induce production of ANCA [19, 20].

*Discussion and conclusion*

In the literature, AAV is often described as a possible adverse drug reaction associated with PTU therapy. Moreover, PTU is one of the drugs most associated with drug-induced AAV.

Hyperthyroidism is often caused by an autoimmune disease, like Grave's disease. These patients also have a tendency to develop other autoimmune conditions. In their review article, Balavoine et al. found that the frequency of ANCA-positive cases in patients with Grave's disease before starting antithyroid drug therapy was relatively low (between 0-13%, compared to 4-64% for patients with PTU therapy). So, although Grave's disease (and other auto-immune diseases) might have a predisposing role, antithyroid drug therapy could also play a role in developing ANCA positivity [10]. Further research is required to assess the causality and mechanism involved in this association.

Stopping the offending drug in time is important to prevent further disease progression and may be sufficient for patients with mild symptoms. Testing for serum ANCA is an effective tool for early diagnosis of drug-induced AAV [9]. Early detection of drug-induced AAV is important to prevent further disease progression. Therefore, attention is warranted for the association between PTU and drug-induced (ANCA-associated) vasculitis.

References


1. *Dutch SPC propylthiouracil 50mg tablets Aurobindo®*. version date 30-11-2020; Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h52546_smpc.pdf.
2. *Informatorium Medicamentorum via KNMP Kennisbank*. 2022; Available from: https://kennisbank.knmp.nl/ (access restricted).
3. *UK SPC propylthiouracil 50mg tablets*. version date 13-03-2020; Available from: https://www.medicines.org.uk/emc/product/3123/smpc#gref.
4. Merkel, P. *Overview of and approach to the vasculitides in adults*. UpToDate (access restricted) 2022 30-03-2021.
5. Yates, M. and R. Watts, *ANCA-associated vasculitis.* Clinical Medicine, 2017. **17**(1): p. 60.
6. Kitching, A.R., et al., *ANCA-associated vasculitis.* Nature Reviews Disease Primers, 2020. **6**(1): p. 71.
7. Nakazawa, D., et al., *Pathogenesis and therapeutic interventions for ANCA-associated vasculitis.* Nature Reviews Rheumatology, 2019. **15**(2): p. 91-101.
8. Argyropoulou, O.D., et al., *Occurrence and Antigenic Specificity of Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (P-ANCA) in Systemic Autoimmune Diseases.* Cells, 2021. **10**(8): p. 2128.
9. Weng, C.H. and Z.C. Liu, *Drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis.* Chin Med J (Engl), 2019. **132**(23): p. 2848-2855.
10. Balavoine, A.S., et al., *Antineutrophil Cytoplasmic Antibody-Positive Small-Vessel Vasculitis Associated with Antithyroid Drug Therapy: How Significant Is the Clinical Problem?* Thyroid, 2015. **25**(12): p. 1273-81.
11. Dolman, K.M., et al., *Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy.* Lancet, 1993. **342**(8872): p. 651-2.
12. *Dutch SPC valsartan 80mg tablets (Diovan®).* Version date 31-12-2020; Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h26939_smpc.pdf.
13. *Dutch SPC ibuprofen 200mg tablets (Nurofen Flextin®)*. Version date 26-11-2020; Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h100658_smpc.pdf.
14. *Dutch SPC diclofenac 25mg tablets Teva®*. Version date 16-10-2020; Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h11985_smpc.pdf.
15. *Dutch SPC naproxen 550mg tablets (Sanias®)*. Version date 28-8-2018; Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h121839_smpc.pdf.
16. *US SmPC propylthiouracil tablets, USP.* Version date 9-2018; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/006188s026lbl.pdf.
17. Deshayes, S., et al., *A Worldwide Pharmacoepidemiologic Update on Drug-Induced Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in the Era of Targeted Therapies.* Arthritis Rheumatol, 2022. **74**(1): p. 134-139.
18. *GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board.* 11-04-2022.
19. Tomkins, M., et al., *Propylthiouracil-induced antineutrophil cytoplasmic antibody-associated vasculitis and agranulocytosis in a patient with Graves' disease.* Endocrinol Diabetes Metab Case Rep, 2020. **2020**.
20. Gao, Y. and M.H. Zhao, *Review article: Drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis.* Nephrology (Carlton), 2009. **14**(1): p. 33-41.


*This signal has been raised on January 20, 2023. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl*