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# A REVIEW ON COMPLICATIONS INDUCED BY ANTI-THYROID DRUGS IN PATIENTS WITH HYPERTHYROIDISM

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## ABSTRACT

Hyperthyroidism is argubly, the commonest among endocrine disorders world wide. There is no exception in India also. Hyperthroidism defined as overactivity of thyroid gland which is different from others, because of their ease in diagnosis, acessibility of medical treatment and realative visiblity of thyroid which offers treatment option from physician. The evidence of anti-thyroid drug induced complications is limited to case reports and spontaneous reporting. So this review aims to quantify the incidence and comparative risks of complications induced by anti-thyroid drugs.

**KEYWORDS:** Hyperthyroidism, anti-thyroid drugs, methimazole, carbimazole, propylthiouracil.

## INTRODUCTION

Hyperthyroidism is a common disease affecting men and women, which is a pathological disorder defined as the production by the thyroid gland of excessive amount of thyroid hormones. The thyroid is a small butterfly shaped gland located at the front of the neck. It produces tetraiodothyronine ($T_4$) and triiodothyronine ($T_3$) which are the two primary hormones that controls the cells use of energy. Hyperthyroidism occurs when thyroid makes too much $T_4$ and $T_3$ or both. Hyperthyroidism is a disorder of various aetiologies, the most common cause (50% to 80%) is Graves disease. Other causes like multinodular goiter, toxic

thyroid adenoma and subacutethyroditis should be evident from history and physical examination. Symptoms include nervousness, anxiety, palpitations, increased appetite, weight loss, increased bowel movements, muscle weakness, irregular mensus in women and the signs are warm, smooth, moist skin and tachycardia at rest.[1] The diagnosis for suspected hyperthyroidism should be confirmed by measurement of serum thyrotropin and total or free thyroxine where normally present at high and low concentrations respectively.[2]

There are mainly three principle treatment options such as anti-thyroid drugs, radioiodine therapy and thyroid surgery, all of which are effective but options differ from the indications for them. Anti-thyroid drugs have been used for more than half a century in the management of hyperthyroidism. The mainstay's of anti-thyroid drug therapy are methimazole, carbimazole and propylthiouracil. The principle mechanism is inhibition of organification of iodide and coupling of iodothyronine and hence synthesis of thyroid hormones. Propylthiouracil also inhibits the peripheral monodeiodination of thyroxine and triiodothyronine. Carbimazole is a prodrug as after absorption it is converted to the active form methimazole, hence reducing the production of the thyroid hormones. These drugs may induce complications like hepatotoxicity, agranulocytosis, polymyositis, hypoprothrombonemia, vasculitis, jaundice, though these drugs may show dissimilar incidence of complications with different underlyimg pathogenic mechanism.[3] Treatment options starts with 10 to 20 mg ofmethimazole once a day or 75 to 100 mg propylthiouracil three times a day. More over larger doses are associated with more side effects, larger doses of methimazole/carbimazole lead to rapid biochemical improvement than smaller doses.[2]

## REVIEW OF LITERATURES

**Wang M T *et al (2014)*[4]** conducted a cohort study on 71399 patients with hyperthyroidism receiving methimazole/carbimazole or propylthiouracil with a follow up of 196 days. Methimazole/Carbimazole and propylthiouracil shows dissimilar incidence rates of hepatotoxicity. Methimazole/carbimazole versus propyl thiouracil had higher incidence rate (3.17/1000 versus 1.19/1000 persons-years) but have a lower incidence rate of acute liver failure (0.32/1000 versus 0.68/1000 persons-years). The relative risk on use of methimazole/carbimazole was associated with a 2.89 fold (95% CI 1.81, 4.60) increased hepatitis risk when compared with propylthiouracil, the risk increasing to 5.08 fold (95% CI 3.15, 8.18) for high dose methimazole/carbimazole. When compared to propylhiouracil the dissimilar incidence of hepatotoxicity caused by methimazole/carbimazole are associated in a

dose dependant manner with an increased risk for hepatitis, while the risks are similar for acute liver failure and cholestiasis.

**Fumiko Otsuka *et al* (2012)**[5] conducted a study on four hundred and forty nine patients with untreated graves disease were randomly assigned to three groups based on type or dosage of anti-thyroid drugs. The type, frequency and onset of side effects were assesed in patient groups taking 15mg/day, 30mg/day methimazole and 300mg/day propylthiouracil. Cutaneous reaction, liver dysfunction and also other side effects were assessed every 2 weeks after starting anti-thyroid administration. The frequency of cutaneous reactions in patients taking 30mg/day methimazole and hepatotoxicity in those taking 300mg/day propylthiouracil were high while the overall frequency of patients taking 15 mg/day methimazole was low. The frequency of side effects did not differ between $2^{nd}$ and $1^{st}$ anti-thyroid drugs. Higher incidence of hepatotoxicity occurred in patients who were switched from methimazole to propylthiouracil because of hepatotoxicity of former. Attention to onset times of side effects and cross reactvity of drugs is required.

**Kobayashi S *et al* (2014)**[6] conducted study on a total of 81 patients who were diagnosed with anti-thyroid drug induced agranulocytosis. Investigated the characteristics of patients who developed agranulocytosis during their second or last course of treatment. Patients were assigned into two groups in which the "first group" consist of 35 patients (methimazole, n=28; propylthiouracil, n=7) developed agranulocytosis during their first uninterrupted course of anti-thyroid therapy and 14 cases (developed agranulocytosis with same anti-thyroid drug in the second or later course of treatment they are designated as "resumed group". No significant difference between groups in terms of granulocyte count, mortality rate and recovery. When therapy is resumed, patient follow up is necessary to monitor the development of agranulocytosis.

**Takata k *et al* (2009)**[7] conducted a retrospective study were 2087 subjects treated with 30mg/d of methimazole and 2739 treated with 15mg/d of methimazole. This study compares the prevalance of methimazole induced agranulocytosis in hyperthyroid patients who are taking methimazole 15mg/day to those who taking 30mg/day of methimazole. The prevalence of agranulocytosis plus neutropenia in 30mg/d group was significantly higher than in 15mg/d group (1.581% versus 0.474% respectively $P<0.001$). It is very likely that methimazole induced agranulocytosis occurs with larger dose of methimazole and is dose

related. Thus this study shows that dose of methimazole should be adjusted considering both effectiveness and risk of side effects.

**Andersen S L *et al* (2013)**[8] conduted a cohort study including 817093 children live-born from 1996 to 2008. The prevalence of birth defects was high in children exposed to anti-thyroid drugs in early pregnancy. Exposure groups are assigned according to maternal anti-thyroid drug use in early stage of pregnancy (Propylthiouracil, n=564; methimazole/carbimazole, n=1097; anti-thyroid drug shifted in early pregnancy, n=159; no anti-thyroid drug use in pregnancy, n=3543; non-exposure, n=811730). High prevalance of birth defects caused in children exposed to ant-thyroid drugs in early pregnancy (methimazole/carbimazole 9.1%, propylthiouracil 8.0%, methimazole/carbimazole and propylthiouracil 10.1%, no anti-thyroid 5.4%, non exposed 5.7% P<0.001) Methimazole/Carbimazole and propylthiouracil were associated with urinary system malformation and propyl thiouracil with malformations in the face and neck region. Choanal atresia, esophageal atresia, omphalocele and aplasia cutis were common in exposed children. The spectrum of malformations differed with different anti-thyroid drugs. This study supports the need for the development of new anti-thyroid drugs with fewer side effects.

**Stine Linding A *et al* (2016)**[9] conducted a population based cohort study on all induviduals registered as the parent of live-born child in Denmark, 1973-2008, were identified (n=2299952) and studied from 1995 upto 2010 for anti-thyroid drug use. In the population studied, 28998 induviduals with redeemed prescription of anti-thyroid drugs (exposure in 2115 pregnancies), which was associated with about 45 cases of agranulocytosis (1 in pregnancy) and 10 cases of liver failure (1 in pregnancy). During 10 year period 41 cases of agranulocytosis and 11 cases of liver failure was identified (agranulocytosis:0.16% of anti-thyroid exposed [methimazole: 0.11% versus propylthiouracil: 0.27%, P=0.02]; liver failure: 0.03% of anti-thyroid exposed [methimazole: 0.03% versus propylthiouracil: 0.05%, P=0.4]). Birth defects was associated with 3.4% of exposed children. By the use of anti-thyroid drugs, 83% of the majority developed side effects within 3 months and 25% during hyperthyroidism relapse, hence birth defects are dominant in pregnancy with the use of anti-thyroid drugs. So this study recommends restricting the use of anti-thyroid drugs in early pregnancy to reduce side effects.

## CONCLUSION

Anti-thyroid drugs induced complications is now a days common in clinical practice as a possible cause of increased morbidity and mortality in patients with hyperthyroidism. This review presents a detailed discussion about the complications that suspected with the use of anti-thyroid drugs in patients with hyperthyroidism. Although effective treatment are available, none is perfect. Thus the best way to decrease complications is to educate patients about common symptoms that may contribute to early diagnosis. Despite the safe profile of drug they cause complications, so a baseline assesment of laboratory parameters before starting an anti-thyroid treatment should be recomendable. Hence attention to onset times of side effects and dose reduction lead to safer treatment. This review points out the need for further research work regarding evidence of anti-thyroid drug induced complications.

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