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AMIODARONE INDUCED THYROTOXICOSIS - REVIEW OF TREATMENT

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ABSTRACT

Amiodarone is derivative of benzofuran. This medicine was classified as class III anti-arrhythmic drug. Amiodarone is indicated to treat ventricular tachycardia and recurrent ventricular fibrillation. This medicine is a narrow therapeutic index. There are need therapeutic drugs monitoring to minimize adverse drug reaction (ADR). One of ADR of amiodarone therapy is amiodarone induced thyrotoxicosis **(**AIT). The review is aimed to determine the therapy of AIT. Review was performed by searching articles published in Pubmed and science direct by typing the keywords of ”therapy" and "amiodaron induced thyrotoxicosis". Prednisone, perchlorate, methimazole and Iopanoic acid (IopAc) are used to treat AIT with various results.

Keywords: Amiodarone, narrow therapeutic index, adverse drug reaction.

Introduction:

Amiodarone is a medicine widely used as anti-arrhythmic. This medicine is indicated to treat atrial ventricular fibrillation and supraventricular tachycardia [1]. Amiodarone is narrow therapeutic index and has large variation in pharmacokinetics individual [2]. The kinetic profile of amiodarone is as follows; The bioavailability of amiodarone varies in 35-65%[3]; Cmax 3-7 hours after administration, onset of action of amiodarone after one dose by IV route is between 1-30 minutes, SSC (Steady-state concentrations) in the plasma 0.4-11.99 µg/ml[4,5]; T Vd (volume of distribution) was 9.26-17.17 L/kg in healthy volunteers and 6.88-21.05 L/kg in the SVT patients[6]; The protein binding of amiodarone is about 96%[4]. Amiodarone is metabolized to desethylamiodarone/DEA (the main metabolite)[4] by the CYP3A4 and CYP2C8 enzymes. Elimination of amiodarone is by hepatic and biliary excretion[4]. Desethylamiodarone (DEA) is found in the urine in a small amount[3].

Due to narrow therapeutix index, amiodararose often cause adverse drug reaction (ADR). One of it is hyrotoxicosis. Amiodarone induced thyrotoxicosis (AIT) usually occurs after amiodarone withdrawal[7].

Prevalence:

AIT presents in 2-12% of patients treated byamiodarone. The incidence varies which is presumably influenced by iodine intake in this population. Several studies show that Central European populations are more frequently exposed to AIT. This is presumably because the population is low in iodine intake [8,9,10].

Mechanism:

Amiodarone inhibit de-iodinasi T4 by 5' monodeiodinase. Amiodarone inhibits the activity of 5 'Type I monodeiodinase and causes inhibition of conversion of T4 to T3. This occurs after several months of amiodarone therapy that causes the decrease in T3 concentrations plasma and tissue, and the increase in the concentration of T4[8, 9, 11].

Amiodarone blocks the entry of thyroid hormones into the cell. The results of the kinetic study demonstrated the transfer of T4 from plasma to tissue as in the heart decreases. This reduces storage of intracellular T4 substrate thereby decreasing T3 production[9, 12].

Therapy:

There are two (2) studies with randomized trial therapy for AIT (table 1)

Table 1. Study of AIT therapy

Study design	Population	Eligible criteria	Treatment/intervention	Outcome	Ref.
Randomized multicenter study	Patiesnt in Dutch hospitals	Patients with AIT type 2 (TSH < 0.4 mU/lt; FT4 > 25 pmol/lt;thyroid peroxidase antibodies<50 kU/lt and TSH	3 group: prednisone + methimazole	TSH ≥ 0.4 mU/lt on initial therapy=12 (100%). TSH ≥0.4 mU/lt on additional therapy= NA Time to FT4≤ 25 pmol/lt (wk)*b*= 4 (4–20) Time to TSH ≥0.4 mU/lt (wk)*b*= 8 (4–20) Recurrent thyrotoxicosis-1 Time of recurrence (wk)= 24 Time to TSH 0.4 mU/lt (wk)=8	(13)

		binding inhibitory immunoglobulins < 2 U/lt; poor or no visualization of thyroid gland on 99mTc-pertechnetate scintigraphy; no nodular goiter (> one nodule or a nodule 1 cm) on USG)	Perchlorate+ methimazol prednisone +perchlorate+ methimazole	TSH ≥0.4 mU/lt on initial therapy=10(71%). TSH ≥0.4 mU/lt on additional therapy= 4(29%) Time to FT4≤ 25 pmol/lt (wk)*b*= 12 (4–20) Time to TSH≥ 0.4 mU/lt (wk)*b*= 14(4–32) Recurrent thyrotoxicosis=0 Time of recurrence (wk)= NA Time to TSH 0.4 mU/lt (wk)=NA TSH ≥0.4 mU/lt on initial therapy=10(100%). TSH ≥0.4 mU/lt on additional therapy= NA Time to FT4≤ 25 pmol/lt (wk)*b*= 8(4–20) Time to TSH ≥ 0.4 mU/lt (wk)*b*= 12(4–28) Recurrent thyrotoxicosis=2 Time of recurrence (wk)= 12 & 76 Time to TSH 0.4 mU/lt (wk)=4	
Randomized prospective	Patients of Pisa university, Italia	Patiens AIT II(biochemical hyperthyroidism; absence of goiter, absence of thyroidal hypervascularization on color flow Doppler sonography (CFDS); low (4%) to undetectable 24-h thyroid radioiodine uptake (RAIU); absence of circulating antithyroglobulin (TgAb), antithyroperoxidase (TPOAb) and anti-TSH receptor (TRAb) antibodies	Iopanoic acid (IopAc) Prednisone	Serum-free T3 (ng/dl)= 0.75± 0.20 to 0.46± 0.10 ng/dl, *P* 0.01 serum FT4=2.90 ±0.6 ng/dl to 2.30± 0.4 ng/dl , *P* 0.39 Serum TSH (U/ml)= normal range after 84 ±43day Serum-free T3 (ng/dl)= 0.58 ± 0.10 ng/dl to 0.34± 0.03 ng/dl *P* 0.003 (7days therapy) serum FT4= 2.70± 0.32 ng/dl - 1.0 ±0.04 ng/dl ng/dl , *P* 0.0001 Serum TSH (U/ml)= normal range after 40 ± 34day	(14)

Discussion

AIT is a problem that often occurs in patients receiving amiodarone treatment. The therapy of AIT among others are prednisone, methimazole, perklorat and iopanic acid[13,14]. Table 2 shows that prednisone, perchlorate, methimazole and iopanoic acid (IopAc) can be used to treat AIT with various results.

Prednisone ($C_{21}H_{26}O_5$) is metabolized in the liver to prednisolone (active form). Prednisolone is a corticosteroid agonist. The molecular weight of Prednisone is 358.4281 (average)[15]. This medicine poses inflammatory process of AIT[16].

Fig 1. Structure of Prednisone[15]

Perchlorate (ClO_4) improves AIT by inhibition uptake of thyroidal iodine thus decreases production of thyroid hormone (T3 &T4) [17]. This medicine has molecular weight 99.451 (average)[18].

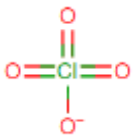

Fig.2 Structure of perchlorate[18]

Methimazole can be used to treat AIT. The main mechanism of action of methimazole is to block the production of thyroid hormone from the thyroid gland thereby preventing the synthesis of thyroxine (T4) and tri-iodothyronine (T3)[19]; interfere with the oxidation of iodide ions and iodothyrosyl groups. This causes a decrease of thyroglobulin and circulating thyroid hormone levels[19, 20]. Methimazole has molecular Weight of 114.169 9 (average)[19].

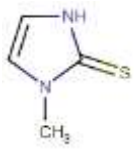

Fig.3 Structure of methimazole[21]

Iopanoic acid belongs to the group of oral cholecystographic agents (OCA). This drug has been used to treat hyperthyroidism because of its fast effect and excellent safety[22-24]. This medicine inhibits deiodination which is responsible for peripheral conversion of T4 to T3[23]. In particular, these agents inhibit the deiodination of the outer ring of T4 to the active metabolites T3, but does not affect the inner ring deiodination from T4 to 3,3 ', 5'-triiodothyronine (reverse T3, rT3)[11]. Reverse T3 (rT3) can inhibit monodeiodination T4 to T3[25]. IopAc controls thyrotoxicosis in the short term due to its peripheral effects[26]. Iopanoic acid has molecular weight of 570.9319[27].

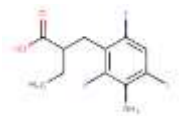

Fig 4. Structure of Iopanoic acid[27]

Conclusion

Therapy of AIT by prednisone, perchlorate, methimazole and Iopanoic acid (IopAc) has various results. Time to FT4 25 pmol/liter (wk) of therapy by prednisone +methimazole is faster 4 (4-20) than Perchlorate+ methimazol and Perchlorate+ prednisone +methimazol. Time to TSH 0.4 mU/liter (wk) of therapy by prednisone +methimazole is faster 8 (4-20) than Perchlorate+ methimazol and Perchlorate+ prednisone +methimazol. Perchlorate and methimazole give the best results in relation to the absence of recurrent toxicity.

IopAc and glucocorticoid therapy can reduce FT3 serum levels rapidly. However, patients treated by IopAc take longer time than patients treated by glucocorticoids therapy to reach normal serum FT4 level. This happens due to the facts that IopAc only exerts its effect on changing T4 to T3 and it does not affect the underlying destructive thyroiditis. IopAc controls thyrotoxicosis in the short term due to its peripheral effects.

Prednisone alone can reduce FT4 level significantly (but not IopAc). It is allegedly prednisone has inhibitory effect on I 5-deiodinase activity and poses inflammatory in thyroid thus reducing serum FT4 levels.

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