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Review Article

Amiodarone and thyroid hormone metabolism

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Introduction

Amiodarone, an antiarrhythmic and anti-anginal agent, contains 75 mg of organic iodine per 200 mg active substance. The drug is deiodinated during its biotransformation, and it is estimated that a dose of 200 mg releases 6 mg of free iodine (Broekhuyzen *et al.*, 1969). Consequently, the thyroid gland has to adjust itself to these pharmacological quantities of iodine. When amiodarone medication is discontinued, it may take months until the iodine excess is cleared from the body due to the very long elimination half-life (approximately 40–60 days) (Haffajee *et al.*, 1983; Plomp *et al.*, 1984). We will review the pharmacological and pathological effects of amiodarone on thyroid hormone metabolism, and discuss the relationship between the thyroidal effects of amiodarone and its mechanism of action.

Pharmacological effects of amiodarone on thyroid hormone metabolism

Short-term amiodarone medication, up to 4 weeks, results in increased plasma thyroxine (T_4), free thyroxine (FT_4) and reverse triiodothyronine (rT_3) concentrations and a decrease in plasma triiodothyronine (T_3) and free triiodothyronine (FT_3); these changes are accompanied with an increase of basal plasma thyrotropin (TSH) and peak TSH levels after TSH-releasing hormone (TRH), mostly within the normal range (Burger *et al.*, 1976; Melmed *et al.*, 1981). Continuation of amiodarone medication is associated with a further rise in plasma T_4, FT_4 and rT_3 and fall in plasma T_3; TSH levels return gradually to pre-treatment values. A steady-state in hormone plasma concentrations is reached after 12–16 weeks (Melmed *et al.*, 1981). Amiodarone has no effect on plasma thyroxine-binding-globulin, nor does it interfere with the radioimmunoassays of thyroid hormones. Short-term amiodarone treatment is associated with a decrease of T_3 and T_4 production rate (PR) and of T_4 metabolic clearance rate (MCR); since the decrease in T_4-MCR is relatively greater than the decrease in T_4-PR, plasma T_4 values increase (Lambert *et al.*, 1982). Long-term amiodarone treatment results in an increased T_4-PR and a decreased T_4-MCR (Lambert *et al.*, 1982). No data are available on rT_3 kinetics in humans, but in rabbits rT_3-MCR is decreased by amiodarone (Kannan *et al.*, 1984).

The initial decrease of T_4-PR can be explained by a transient inhibition of thyroid hormone secretion by the iodine excess derived from amiodarone (Vagenakis *et al.*, 1973). The reduction in MCR of rT_3 and T_4 and the decrease in PR of T_3 appears to be caused by inhibition of type 5-deiodinase, the enzyme that catalyses $T_4 \rightarrow T_3$ and $rT_3 \rightarrow 3,3'\text{-}T_2$ deiodination in liver. The generation of T_3 out of added T_4 is markedly reduced in a dose-related manner in liver homogenates from rats pretreated *in vivo* with amiodarone (Balsam & Ingbar, 1978; Sogol *et al.*, 1983). If amiodarone is added *in vitro* the T_3 production from T_4 is inhibited when isolated rat hepatocytes are used (Aanderud *et al.*, 1984), but not when liver homogenates are used (Sogol *et al.*, 1983). This suggests that the effect of amiodarone is mediated via the plasma membrane. Indeed, amiodarone inhibits thyroid hormone uptake by rat hepatocytes in primary culture (Krenning *et al.*, 1982). One might therefore hypothesize that amiodarone primarily inhibits tissue uptake of thyroid hormones, notably in the liver. This would explain the decrease in rT_3-MCR (the liver is an important site of rT_3 degradation – Silva *et al.*, 1982), in T_4-MCR (sequential deiodination of T_4 is the major pathway of T_4 degradation – Engler & Burger, 1984), and in T_3-PR (by decreased availability of the substrate T_4 – the liver is a major production site of T_3).

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Pathological effects of amiodarone on thyroid hormone metabolism

Diagnosis of amiodarone-induced thyrotoxicosis (AIT) and amiodarone-induced hypothyroidism (AIH)

Whereas the clinical and laboratory diagnosis of AIH poses no special problems, the diagnosis of AIT can be very difficult. Firstly, the anti-adrenergic effects of amiodarone might moderate the clinical signs and symptoms of thyrotoxicosis. Secondly, the diagnostic accuracy of thyroid hormone assays in plasma is decreased, as is obvious from Figure 1. Patients with an exaggerated TSH response to TRH had either a decreased plasma T_4 (group III B, in all cases associated with overt myxoedema) or no decreased plasma T_4 (group III A, associated with a clinically euthyroid state; these patients represent cases of subclinical hypothyroidism) (Evered *et al.*, 1973). The normal TRH-responders (group I) were all clinically euthyroid, despite grossly elevated T_4, FT_4 index and FT_4 values. Patients with a subnormal TSH response to TRH (group II) were judged to have overt thyrotoxicosis (group II B) or subclinical hyperthyroidism (group II A) by the presence or absence of signs and symptoms of thyrotoxicosis.

It is obvious that none of the thyroid function tests completely discriminates between the groups II B and II A. Thus, laboratory diagnosis of thyroid function

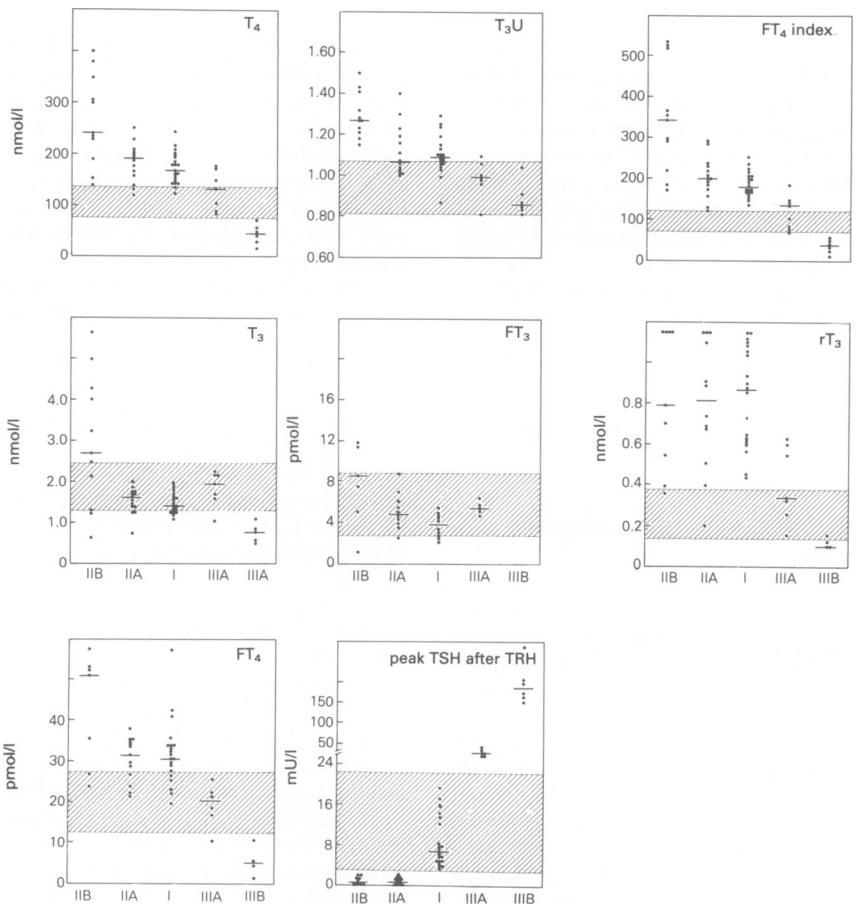

Figure 1 Individual and median values of plasma thyroid hormone concentrations of 59 patients on long-term amiodarone therapy, divided according to their TSH-response to 200 μg TRH i.v. (group I = normal, group II = decreased, and group III = increased response) and their clinical state (group A = euthyroid, group B = dysthyroid). Hatched areas indicate reference range of normal values, as obtained by RIA in 63 healthy volunteers in case of T_4, T_3U, FT_4 index, T_3, rT_3 and TSH response to TRH (Wiersinga & Touber, 1980) or as indicated by manufacturer in case of FT_4 (Corning Immo Phase FT_4 kit) and FT_3 (Amerlex-M Free T_3 RIA kit).

remains inconclusive in some patients, and clinical judgment must tell if they do or do not need antithyroid treatment. The introduction of the ultrasensitive immunoradiometric assay of TSH (TSH-IRMA) might greatly facilitate the laboratory diagnosis of thyroid function, since undetectable TSH-IRMA values are observed only in (subclinical) hyperthyroidism and reliably predict an absent TSH response to TRH (Seth *et al.*, 1984). Consequently, if there is a detectable TSH-IRMA concentration in plasma in amiodarone-treated patients not exceeding the upper normal limit, no further action is needed; in the case of undetectable TSH-IRMA values, overt thyrotoxicosis is indicated by increased T3 or FT3 values but not excluded by normal T3 or FT3 values (Wiersinga *et al.*, 1986).

Incidence of AIT and AIH

In a prospective Belgian study (Chevigné-Brancart *et al.*, 1983) the incidence of AIT was 15.3% and AIH 8.5%. Interestingly, 80% of the hypothyroid cases occurred in the first year of amiodarone treatment in contrast with 30% of the hyperthyroid cases; after discontinuation of amiodarone treatment no new cases of hypothyroidism but five new cases of hyperthyroidism (17%) were observed within 6 months. An absent TSH response to TRH was encountered in 32% of patients who remained clinically euthyroid. Another intriguing study related the incidence of amiodarone-induced dysthyroidism to dietary iodine intake (Martino *et al.*, 1984b): in iodine-deplete areas, AIT is more prevalent than AIH, whereas in iodine-replete areas there exists a preponderance of hypothyroid over hyperthyroid cases.

Pathogenesis of AIT and AIH

The pathogenesis of iodine-induced dysthyroidism is essentially unknown. The degree of iodine excess is similar in euthyroid, hyperthyroid and hypothyroid patients on long-term amiodarone therapy (Trip *et al.*, 1983; Eason *et al.*, 1984) and is therefore not the determinant *per se*.

Some pre-existent thyroid abnormality may be unmasked by iodine excess, and the likelihood of such a mechanism in AIH is substantiated by its development relatively early in the course of treatment and by its preponderance in females (autoimmune thyroiditis is more common in women than in man). The precipitation of overt hyperthyroidism by iodine excess in patients with previous thyroid abnormalities is also well known (Fradkin & Wolff, 1983), but it cannot be denied that iodide-induced hyperthyroidism also occurs in patients in whom, after recovery, thyroid function and regulation appears to be perfectly normal (Savoie *et al.*, 1975). The steady appearance of new hyperthyroid cases with continuation of

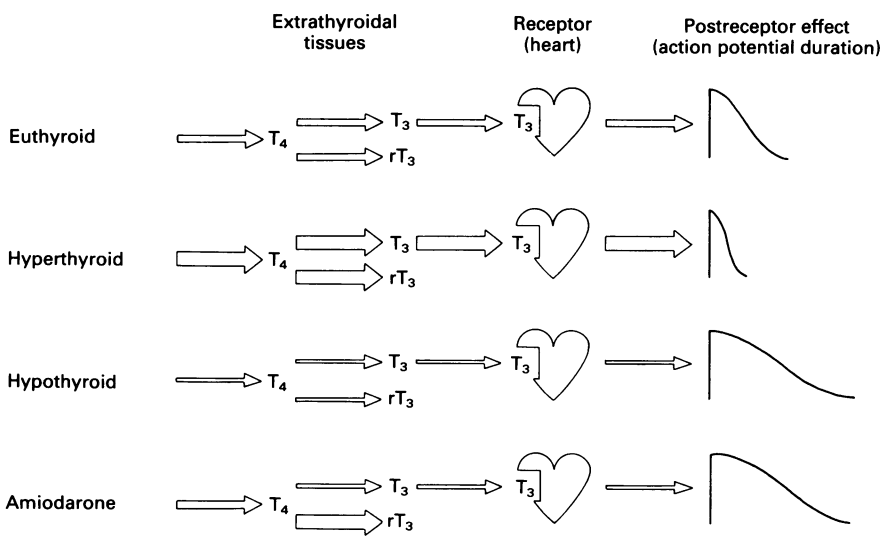

Figure 2 A hypothetical scheme on the mechanism of action of amiodarone by the induction of a local 'hypothyroid-like' condition in the heart. The duration of cardiac action potentials is viewed as a postreceptor effect of nuclear T_3-receptors in the heart. Receptor occupancy is decreased in hypothyroid and in amiodarone-treated patients, resulting in an identical lengthening of the action potential (modified according to Nademanee *et al.*, 1983).

amiodarone therapy (Chevigné-Brancart *et al.*, 1983) also indicates a different pathogenesis in this group of patients, which remains unexplained. Lastly, iodine may facilitate the development of autoimmune thyroid disease (McGregor *et al.*, 1985): 55% of patients taking amiodarone for 30 days developed thyroid microsomal antibodies (Monteiro *et al.*, 1986).

Treatment of AIT and AIH

Discontinuation of amiodarone medication is the most logical approach in the treatment of AIT and AIH, but is not always feasible because of the presence of cardiac disease requiring amiodarone treatment. The management of AIH is relatively easy: withdrawal of amiodarone, and/or T_4 substitution. Management of AIT is more difficult, mainly because of a lower effectiveness of antithyroid drugs and radioactive iodine during iodine excess. Thyroidectomy is a rigorous treatment for a self-limiting disease and may carry a high operative risk in these cardiac patients. Spontaneous cure in non-treated cases is observed within an average of 6 months; a phase of slight hypothyroidism precedes the return to euthyroidism (Léger *et al.*, 1984).

High doses of prednisone, up to 60 mg/day, are reported to have a dramatic effect, with a return of plasma T_4 and T_3 to normal values in 2 weeks (Staübli *et al.*, 1981; Wimpfheimer *et al.*, 1982; Léger *et al.*, 1984). Recently, a combination of methimazole (40 mg/day) and potassium perchlorate (1 g/day until euthyroidism is reached) has been advocated (Martino *et al.*, 1984a). Inhibition of iodine uptake by perchlorate results in a greater effectiveness of methimazole, and 8 out of 9 patients thus treated were euthyroid within 45 days. Potassium perchlorate may also be useful in AIH: euthyroidism was reached in 3 months by discontinuation of amiodarone, but in 15–20 days if potassium perchlorate was given (Martino *et al.*, 1985).

Relation of thyroid hormone effects of amiodarone to its mechanism of action

The pharmacological actions of amiodarone include bradycardia, depression of myocardial oxygen consumption and lengthening of the cardiac action potential (Singh & Vaughan Williams, 1970). The lengthening of the cardiac action potential can be prevented by concomitant administration of a physiological dose of T_4 (Singh & Vaughan Williams, 1970), and an identical change of cardiac action potentials has been observed in thyroidectomized rabbits (Freedberg *et al.*, 1970). Also, the electrocardiographic changes in amiodarone-treated patients resemble those in hypothyroid patients (Staübli *et al.*, 1981). It has therefore been hypothesized that one of the mechanisms of action of amiodarone is the induction of a local 'hypothyroid-like' condition in the extrathyroidal tissues, notably in the heart (Freedberg *et al.*, 1970). A decreased production of T_3 out of T_4 by inhibition of 5'-iodiothyronine-deiodination might result in a decreased receptor occupancy of nuclear T_3 receptors and thereby in modulation of postreceptor effects of T_3 (e.g. the duration of the action potential). The hypothesis (Figure 2) could account for both the anti-anginal and anti-arrhythmic actions of the drug. In favour of this proposed mechanism is the decreased nuclear T_3 receptor occupancy in livers of amiodarone-treated rats (own unpublished observations) and the antagonistic effect of amiodarone on nuclear binding of T_3 in rat thyrotrophs *in vitro* (Franklyn *et al.*, 1985). The hypothesis is not supported by recent studies with iopanoic acid, a drug that also effectively inhibits the conversion of T_4 into T_3 but had no antiarrhythmic activity in man (Meese *et al.*, 1985).

Indirect evidence for the hypothesis can be deduced from a study in patients with ventricular arrhythmias: an increase in basal and TRH-stimulated plasma TSH and a lengthening into the hypothyroid range of systolic time intervals was present in amiodarone-responders but not in amiodarone-nonresponders (Beck-Peccoz *et al.*, 1985). Also, serum rT_3 levels are correlated with amiodarone efficacy in the treatment of refractory arrhythmias (Nademanee *et al.*, 1982; Gonska *et al.*, 1985), with serum amiodarone levels (Anastasiou-Nana *et al.*, 1984) and with the QTc interval (Borghi *et al.*, 1983).

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