PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **181**, 233–236 (1986)

Effects of Desethylamiodarone on Thyroid Hormone Metabolism in Rats: Comparison with the Effects of Amiodarone (42246)

NAGAMMAL VENKATESH, LENA AL-SARRAF, JEROME M. HERSHMAN, AND BRAMAH N. SINGH

Department of Medicine, Division of Cardiology, Wadsworth V.A. Medical Center, Los Angeles, California 90024

Abstract. Desethylamiodarone is the principal metabolite of amiodarone. Amiodarone is a class III antiarrhythmic agent, which acts by lengthening repolarization in the myocardium, an effect that is identical to that produced by hypothyroidism. Amiodarone is known to alter thyroid hormone metabolism, and it has been suggested that the mechanism underlying its antiarrhythmic action is the induction of a myocardial but not generalized hypothyroidism. Since the serum levels of desethylamiodarone reach those of the parent compound during chronic amiodarone therapy, it has been suggested that at least part of amiodarone's pharmacological effects may be attributable to the additive effects of the metabolite. Therefore, we investigated the effects of desethylamiodarone on thyroid hormone metabolism and compared them with those of amiodarone in rats. We have shown that chronic treatment with desethylamiodarone decreased serum T_3, markedly increased serum reverse T_3 with no significant change in serum T_4. These effects are similar to those of amiodarone. The data suggest that the chronic effects of amiodarone on thyroid hormone metabolism may be due at least in part to the actions of desethylamiodarone.

Amiodarone hydrochloride, a benzfuran derivative, has antiarrhythmic as well as antianginal actions (1). The drug aborts and prevents arrhythmias by selectively lengthening cardiac repolarization (1), an effect similar to that observed in rabbits made hypothyroid by thyroidectomy (2). It is known that arrhythmias are uncommon in hypothyroidism and common in hyperthyroidism (3). Numerous studies have shown that chronic administration of amiodarone alters thyroid function, causing significant increases of serum thyroxine (T_4),[1] minor but significant decreases in triiodothyronine (T_3), and significant increases in serum reverse triiodothyronine (rT_3) (4). The electrophysiologic effects of amiodarone are negated by the concomitant administration of thyroid hormone (1). It has been suggested that a drug-induced hypothyroid state of the myocardium, which has some specificity (1), may constitute one of the mechanisms for the drug's antiarrhythmic actions (5) because generalized hypothyroidism is not produced.

Amiodarone has two iodine atoms in its molecule; iodine comprises 37% of its total molecular weight (5). Desethylamiodarone, the principal metabolite of amiodarone that is formed in amounts equal to those of the parent compound during chronic therapy (6), has a similar chemical structure except for the absence of an ethyl group (Fig. 1). We have shown that desethylamiodarone has many pharmacologic properties similar to those of amiodarone, such as the antiadrenergic effects (unpublished data from Venkatesh *et al.*) and an interaction with digoxin during combination therapy (unpublished data from Venkatesh *et al.*). However, whether it influences thyroid hormone metabolism as does the parent compound and contributes to its overall pharmacologic action in this regard is not known. We hypothesized that, because of the similarities in structure as well as pharmacologic effects between the metabolite and the parent compound, desethylamiodarone might influence thyroid hormone indices in a manner similar to that of amiodarone. The effects of chronic desethylamiodarone therapy on serum thyroid hormone levels were therefore studied in rats, and the results were compared with those following chronic amiodarone therapy.

Materials and Methods. *Experimental design.* Male Fisher-344 rats weighing 300–400 g were used in the study. Rats were divided

[1] Abbreviations used: T_4, thyroxine; T_3, triiodothyronine; rT_3, reverse triiodothyronine; HPLC, high-pressure liquid chromatography; RIA, radioimmunoassay.

0037-9727/86 $1.50

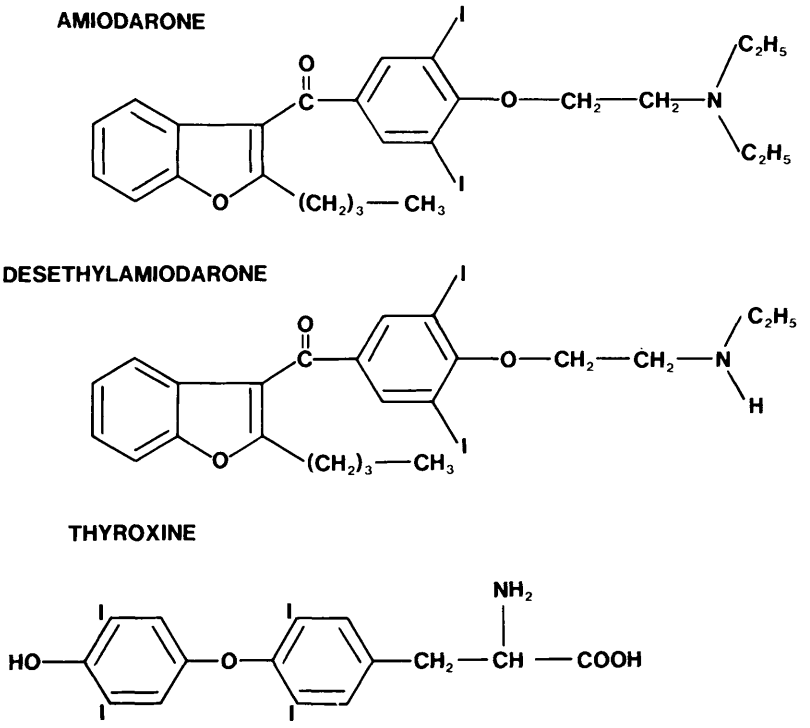

FIG. 1. Chemical structures of amiodarone, desethylamiodarone, and thyroxine. Note the structural similarities among the three compounds.

into three groups. Group I (n = 9) was given 1 ml of deionized distilled water per day orally for 14 days. Group II (n = 6) was treated with 100 mg/kg/day desethylamiodarone for 14 days. Group III (n = 5) was treated with 100 mg/kg/day of amiodarone for 14 days. One milliliter of amiodarone and desethylamiodarone were administered as 3% solutions in deionized distilled water by gavage. After these drugs had been given, the rats were anesthetized with diethyl ether, blood samples were obtained from the abdominal aorta, and the animals were killed. Sera obtained from the blood samples were analyzed to determine the concentrations of the following: T_4, T_3, rT_3, desethylamiodarone, and amiodarone.

Determination of serum concentrations of thyroid hormones. Commercially available RIA kits were used. Serum T_4 and T_3 were determined by using the RIA kit obtained from Corning (Corning, N.Y.). Serum rT_3 was determined by using RIA kit obtained from Serono (Braintree, Mass.).

Determination of serum concentration of desethylamiodarone and amiodarone. The methods utilized were those described by Flanagan *et al.* (7). To 200 μl of serum sample, 20 μl of 2 *M* phosphate solution (pH 4.5) containing the internal standard fenethezine was added. The sample was then mixed with 200 μl of diisopropyl ether for 30 sec using a Vortex mixer. One hundred microliters of the extract was then dried under nitrogen, reconstituted in 25 μl of methanol (HPLC grade) and analyzed on a microparticulate (5 μm) silica column using methanol:diethyl ether (85:15) containing perchloric acid (0.02% v/v) as the mobile phase, and the absorption of the effluent was monitored using an ultraviolet detector at 240 n*M*.

Statistical analysis. Unpaired Student's t test was used to determine the significance of the differences of the means of the various groups. Value of $P < 0.05$ was considered to be significant. Groups II and III were individually compared with Group I and with each other.

Results. The mean serum desethylamiodarone concentration for the animals treated with desethylamiodarone chronically (Group

II) was 1.82 ± 0.56 (SD) μg/ml. The mean serum concentrations of amiodarone and desethylamiodarone for the animals treated with amiodarone chronically were 4.15 ± 1.28 and 1.10 ± 0.64 μg/ml, respectively. The mean data on the effects of amiodarone and desethylamiodarone administration on thyroid hormone indices compared to control are shown in Fig. 2. The serum T_3 in the control group was 4.7 ± 0.79 μg/ml. In the desethylamiodarone-treated group, it was 2.66 ± 1.56 μg (−43%; $P < 0.05$); in the case of the amiodarone-treated group it was 3.68 ± 0.43 μg/ml (−22%; $P < 0.05$). Serum rT_3 was increased significantly with the drug treatments. Desethylamiodarone-treated rats showed a rT_3 serum level of 40.6 ± 15.6 pg/ml ($P < 0.001$) and amiodarone-treated rats had a rT_3 serum level of 50.0 ± 20.3 pg/ml ($P < 0.001$) compared to the controls where only traces of rT_3 (below the sensitivity range of the assay) were found. Serum T_4 concentrations following desethylamiodarone and amiodarone treatments were 4.36 ± 1.05 and 4.98 ± 1.23 μg/dl, respectively; compared to the value of 4.22 ± 1.22 μg/dl of the controls, the differences were not statistically significant.

Discussion. Desethylamiodarone is the principal metabolite of amiodarone. During chronic amiodarone therapy desethylamiodarone in amounts equal to those of the parent compound is formed (6). It is known that the cardiac pharmacologic actions following chronic amiodarone administration are complex and at least in part resemble those demonstrated in hypothyroidism (5). If the actions of the metabolite were similar to those of the parent compound, an additive effect of desethylamiodarone may be evident during chronic therapy with the parent compound.

Freedberg *et al.* (2) showed that in rabbits made hypothyroid by thyroidectomy, uniform lengthening of atrial repolarization was seen with a converse effect in hyperthyroidism. Singh and Vaughan Williams (1) showed that chronic administration of amiodarone produced an identical effect on repolarization in rabbit atrial and ventricular action potentials. Such an electrophysiologic effect of amiodarone could be abolished by the concomitant administration of thyroxine (1) suggesting an interrelationship between thyroid hormone and amiodarone actions. Amiodarone is known to decrease serum T_3 (but not into the hypothyroid range) and to increase rT_3 and T_4 during chronic therapy in man (5) and in rabbits (unpublished data from Venkatesh *et al.*). This overall effect is consistent with the

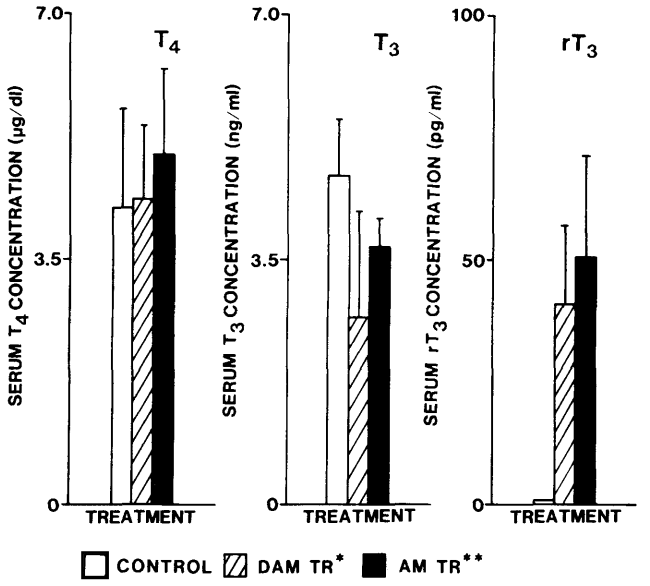

FIG. 2. Changes in the serum levels of T_4, T_3, and rT_3 following chronic treatments with desethylamiodarone and amiodarone are compared to those of the control animals. Values are presented as means ± SD. * Desethylamiodarone treatment; ** amiodarone treatment.

inhibition of the peripheral conversion of T_4 to T_3 (5, 8) but in itself, it does not account for the amiodarone-induced lengthening of the action potential duration similar to that occurring in hypothyroidism. Since the cardiac electrophysiologic effects of hypothyroidism and chronic amiodarone administration are identical, and the drug does not cause generalized hypothyroidism, it has been postulated that it may exert a cardiospecific inhibition of thyroid hormone action (1, 5).

Desethylamiodarone appears to have a similar pharmacologic profile as amiodarone given acutely; it exhibits an antiadrenergic effect equipotent to that of amiodarone (unpublished data from Venkatesh *et al.*). We have also shown that the metabolite alters the kinetics of digoxin in a manner similar to that of the parent compound during combination therapy (unpublished data from Venkatesh *et al.*). Whether the compound has a similar effect on the thyroid hormone metabolism was not clear. Our work clearly demonstrates that the metabolite has almost an identical influence on thyroid hormone metabolism. Therefore, the electrophysiologic effects and the effects on thyroid hormone metabolism brought about by chronic administration of amiodarone, at least in part, may be attributed to the additive effects of its metabolite.

The precise mechanism whereby amiodarone and its metabolite exert their myocardial effects remains uncertain. However, because of their structural similarities to the thyroid hormones, it has been hypothesized that amiodarone and its metabolite may compete directly for the T_3 binding sites in the nuclear membrane (9). This effect may account for amiodarone's known effect of homogeneously lengthening cardiac repolarization. However, the chronic effects of desethylamiodarone on myocardial electrophysiology have not been shown. Preliminary studies in our laboratory indicate acute or chronic administration of the metabolite to rabbits has similar effects on cardiac action potentials as amiodarone, with chronic treatment resulting in a more pronounced effect and acute treatment showing minimal changes.

In summary, we have shown that desethylamiodarone has similar effects on thyroid hormone metabolism as the parent compound. The data provide further support for the possibility that the chronic electrophysiologic effects of desethylamiodarone are similar to those of amiodarone being mediated through the induction of a hypothyroid state in the myocardium.

We are grateful to Dr. Kannan and Ms. Miller for determining the serum levels of amiodarone and desethylamiodarone. We are indebted to Lawrence Kimble for secretarial assistance.

1. Singh BN, Vaughan Williams EM. The effect of amiodarone, a new antianginal drug, on cardiac muscle. Brit J Pharmacol **39**:675, 1970.
2. Freedberg AS, Papp GJ, Vaughan Williams EM. The effect of altered thyroid state on atrial intracellular potentials. J Physiol **207**:357, 1970.
3. Johnson PN, Freedberg AS, Marshall JM. Action of thyroid hormone on the transmembrane potentials from sino atrial nodal cells and atrial muscle cells in isolated atria of rabbits. Cardiology **58**:273–289, 1973.
4. Jonckheer MH, Plockx P, Broechaert I. Low T_3 syndrome in patients chronically treated with an iodine containing drug amiodarone. Clin Endocrinol **9**:27, 1978.
5. Singh BN, Nademanee K. Amiodarone and thyroid function: Clinical implications during antiarrhythmic therapy. Amer Heart J **106**(4):857, 1983.
6. Holt DW, Tucker GT, Jackson PR, *et al.* Amiodarone pharmacokinetics. Amer Heart J **106**(4):840, 1983.
7. Flanagan RJ, Storey GCA, Holt DW. Rapid high performance liquid chromatographic method for the measurement of amiodarone in blood plasma or serum at the concentrations attained during therapy. J Chromatogr **187**:391, 1980.
8. Sogol PB, Hershman JM, Reed AW. The effects of amiodarone on serum thyroid hormones and hepatic thyroxine 5′-monodeiodination in rats. Endocrinology **113**:1464–1469, 1983.
9. Wiersinga WM, Broenik MM. In Vitro Inhibition of Nuclear Thyroid Hormone Binding by Amiodarone and Desethylamiodarone in Rat Liver and Cardiac Muscle. 59th American Thyroid Association, New Orleans, Oct 5th–8th 1983. [Abstract 36]

Received March 5, 1985. P.S.E.B.M. 1986, Vol. 181.
Accepted October 8, 1985.