Atrial fibrillation and hyperthyroidism: a new look at their relationship and therapy with lidoflazine

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Summary

Various kinds of dysrhythmias are found in association with hyperthyroidism but especially atrial fibrillation. The causal relationship of chronic atrial fibrillation and the endocrine disorder is controversial, as is its therapeutic management. Six patients with this particular combination of disorders were treated with lidoflazine: a new anti-anginal drug with anti-arrhythmic activity. All six patients returned to sinus rhythm on lidoflazine treatment although still hyperthyroid and remained in sinus rhythm during the follow up period ranging from 5 to 14 months. This occurred independently of antithyroid treatment. Some evidence is put forward that dysrhythmias and most commonly chronic atrial fibrillation are triggered off by hyperthyroidism or other disorders but that they are maintained by permanent cardiac damage due to arteriosclerosis, hypertension, coronary heart disease or rheumatic valve disease.

Successful chemical cardioversions and maintenance of sinus rhythm can be obtained independent of the thyroid function. Our results confirm the anti-arrhythmic activity of lidoflazine.

Introduction

Hyperthyroidism has been found to be associated not only with sinus tachycardia, one of its features, but also with several dysrhythmias and conduction disturbances such as atrial flutter (Ernstene, 1938), first and second degree of a.v. block (Cookson, 1959; Blizzard and Rupp, 1960; Hoffman and Lowrey, 1960; Rosenblum and Delman, 1963; Lanfranchi and Fauchier, 1973), third degree of a.v. block (Davis and Smith, 1933; Steuer, 1936;

Muggia, Stjernholme and Houle, 1970; Stern, Jacobs and Duncan, 1970; Kernoff, Rossouw and Kennelly, 1972), reversible bundle branch block (Digilio, 1938), ventricular ectopic beats (Rohrbach, 1968), ventricular tachycardia (Ernstene, 1938; Fairhurst and Sash, 1959; Lyngborg and Jacobsen, 1972) and ventricular fibrillation (Boone, 1945; Lyngborg and Jacobsen, 1972). These dysrhythmias, although some are rare, have been described in patients of over 40 years of age who also had coronary artery disease, hypertension or acute infections. Ernstene (1938) found 207 patients with atrial fibrillation among 1000 patients with hyperthyroidism, Bourel *et al.* (1969) twenty-four of eighty-three patients, Rohrbach (1968) four of eleven patients with masked hyperthyroidism, Sandler and Wilson (1959) eighty-four of 462 patients and Jervell (1952) fifty-three of 279 patients. Therefore, atrial fibrillation can be considered as the most common cardiac dysrhythmia associated with hyperthyroidism (Friedberg, 1966; Miyahara *et al.*, 1969). It is common experience that no parallelism exists between heart rhythm and the severity of thyroid dysfunction (Friedberg, 1966). Sinus rhythm is not always restored by normalizing the thyroid function and DC shock, quinidine or combination of drug therapy is often required to restore sinus rhythm.

Lidoflazine, a new anti-anginal drug, has been shown to have anti-arrhythmic activity, especially as concerns supraventricular dysrhythmias such as atrial fibrillation and flutter, in patients with arteriosclerosis, rheumatic heart disease, hypertension, congenital heart disease and lone atrial fibrillation (Miyahara *et al.*, 1969; Piessens, Kesteloot and De Geest, 1970; Schlepper and Derro, 1972; Batlouni, unpublished report; De Vil and Bruyneel, 1974).

We have for the first time treated patients with

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TABLE 1. Summary of the clinical, biochemical and therapeutic information from the six case reports

Subject	1	2	3	4	5	6
Sex	M	F	F	M	F	F
Age	68	70	72	62	44	60
Clinical picture	Hyperthyroidism; diabetes; arteriosclerosis; enlarged heart	Hyperthyroidism; strumectomy at 66 years; calcified aortic atheroma	Hyperthyroidism; strumectomy at 41 years; aortic abdominal aneurysm	Hyperthyroidism; struma; chronic bronchitis; arteriosclerosis	Hyperthyroidism; systolic murmur	Hyperthyroidism; systolic murmur; arteriosclerosis
ECG	Atrial fibrillation 160/min; QRS normal	Atrial fibrillation 90/min; QRS normal; ST depression; T negative	Atrial fibrillation 130/min; QRS normal	Atrial fibrillation 120/min; QRS normal; ST depression; T negative	Atrial fibrillation ventricular ectopic beats 150/min; QRS normal	Atrial fibrillation 100/min; complete left bundle branch block
Blood pressure mmHg	210/80	160/90	200/100	195/105	165/70	155/75
Heart failure	—	+	—	+	—	—
Diuretics	—	Intermittent	—	Intermittent	—	—
Digitalis	+	+	+	+	—	—
Duration atrial fibrillation before lidoflazine	3 months	4 months	At least 1 week	12 months	At least 1 week	29 months
Thyroid condition time of lidoflazine dose	hyper	eu	hyper	eu	hyper	eu
Lidoflazine cardioversion therapy	60 mg b.i.d.	60 mg t.i.d.	60 mg t.i.d.	60 mg t.i.d.	60 mg t.i.d.	60 mg b.i.d.
Duration cardioversion	Half a day	5 days	5 days	6 weeks	4 weeks	2 days
Thyroid treatment	Methyl-mercaptimidazole 10 mg t.i.d. 2 weeks after sinus	Methyl-mercaptimidazole after sinus rhythm	Methyl-mercaptimidazole 2 × 10 mg t.i.d., lugol 10 mg t.i.d. for 1 week	Methyl-mercaptimidazole for 11 months	Radioactive iodine, 3 months before Strumazol simultaneous with lidoflazine	Methyl-mercaptimidazole for 29 months
Plasma K meq/l	4.15	3.5	4.3	4.2	4.9	4
Oral K syrup	—	+	—	—	+	+
Condition	Inpatient	Inpatient	Inpatient	Outpatient	Outpatient	Outpatient

chronic atrial fibrillation and hyperthyroidism with lidoflazine. It is the purpose of this study to demonstrate that lidoflazine converts atrial fibrillation during the hyperthyroid as well as the euthyroid state, and maintains sinus rhythm independent of the thyroid function.

Material and methods

Six consecutive patients with chronic atrial fibrillation and hyperthyroidism were treated with lidoflazine tablets to obtain sinus rhythm. Atrial fibrillation was considered to be chronic when lasting continuously for at least 1 week without any previous attacks of self-limiting atrial fibrillation or palpitations in the history. Special attention was given to the potassium metabolism of the patients. Potassium syrup (20 mEq potassium t.i.d.) was generally given to all patients who had diuretics, laxatives, mild heart failure, ventricular ectopic beats on the resting ECG or low serum potassium value.

Patients with manifest heart failure, special diets (low salt, low calorie) or acute coronary artery disease were excluded unless conditions were altered. No other anti-arrhythmic drug was given except digitalis when required in the presence of heart failure or fast ventricular rhythm at rest (> 100 beats/min).

Lidoflazine tablets of 60 mg were given, starting with one tablet a day during the first week with a weekly increase of one tablet up to three tablets a day for the outpatients. The treatment was started with two or three tablets a day at once for the inpatients. Anti-hyperthyroid treatment was started before or after the cardioversion. The cardioversion was initially attempted in the hospital but later as an outpatient treatment. Hyperthyroidism was believed to be present according to the clinical features and symptoms and when plasma cholesterol was below 150 mg%, PBI above 9%, basal metabolism above +30%, T_3 resin uptake above 35%, T_4 above 12 mg%.

Atrial fibrillation and sinus rhythm were diagnosed by means of repetitive 12-lead ECG recordings at rest. Lidoflazine treatment was maintained at the dose of cardioversion or less for each patient.

Results

Sinus rhythm was obtained in all six patients within half a day to 6 weeks (see Table 1). None of the patients had a history of arterial embolism or signs of mitral valve disease. Anticoagulants were given to one patient only (case 2).

Case 1

The patient continued her treatment of digitalis, lidoflazine 60 mg b.i.d., meprobamate and methyl-

mercapto-imidazole. She has remained in sinus rhythm for 8 months despite two relapses of hyperthyroidism when she stopped methyl-mercapto-imidazole (Strumazol®) therapy.

Case 2

The patient was treated with digitalis, methyl-mercapto-imidazole and lidoflazine 60 mg t.i.d. Follow-up not possible after discharge from hospital.

Case 3

The patient has remained in sinus rhythm for 14 months with lidoflazine 60 mg b.i.d. and lugol solution, although she remains slightly hyperthyroid.

Case 4

The patient remained in sinus rhythm for 5 months taking only one tablet of lidoflazine a day during the last month. Such a low dosage treatment was considered to be ineffective and stopped. Atrial fibrillation promptly returned and remained for another 4 months. The patient, who suffered from character disturbances, refused to take lidoflazine tablets again. He died 12 hr after a trauma from multiple bone and skull fractures.

Cases 5 and 6

Both patients have remained in sinus rhythm for 5 months while taking lidoflazine 60 mg b.i.d. and methyl-mercapto-imidazole.

Discussion

The initial results of converting atrial fibrillation to sinus rhythm and maintaining the rhythm during mild to moderate severe hyperthyroidism look promising although our series is rather small. No rhythm disturbances have been observed or mentioned by the patients but continuous ECG monitoring has not been undertaken during the cardioversion period. No side effects or complications were noticed. Similar cardioversion results of atrial fibrillation to sinus rhythm during hyperthyroidism have been reported with quinidine (De Vil and Bruyneel, 1974) and quinidine with propranolol (Levi and Proto, 1972). Therefore it is difficult to agree with other authors (Carlier, 1973) who consider attempts to convert atrial fibrillation during hyperthyroidism to be utopian since sinus rhythm will not remain so long as hyperthyroidism exists, and most patients convert spontaneously to sinus rhythm once hyperthyroidism is effectively treated (Schrire, 1971; Carlier, 1973). Ernstone (1938) found that of sixty cases of established atrial fibrillation, thyroidectomy resulted in a spontaneous re-establishment of sinus rhythm in twenty-one patients within 10 days after surgery. Subsequently, quinidine sulphate was started in twenty patients,

which converted atrial fibrillation to sinus rhythm in twelve. Six patients of the remaining group died with atrial fibrillation and thirteen others persisted in their dysrhythmia.

Silver, Delit and Eller (1962) found atrial fibrillation to be present in 51% of the patients with thyrocardiac disease before and in 24% after radioactive iodine therapy.

Bock and Klein (1972) found dysrhythmias in fourteen of thirty-eight patients with hyperthyroidism who were more than 60 years old. Tachyarrhythmias were frequent during, as well as after, radioactive iodine therapy, and generally resistant to drug therapy. The authors very seldom observed a spontaneous remission to sinus rhythm in this age group.

Several authors (Ernstene, 1938; Boone, 1945; Jervell, 1952; Moe, 1968; Ticzon and Whalen, 1973) have pointed out that atrial fibrillation may occur as an acute self-limiting form triggered off by hyperthyroidism, pericarditis, pneumonia, influenza, pulmonary embolus, post-thoracotomy, gall bladder disease, alcohol or heroin intoxication. This atrial fibrillation remains chronic and refractory when permanent cardiac damage (with or without atrial enlargement due to rheumatic heart disease, hypertension, arteriosclerosis and coronary heart disease) is present. This explains why 75% of 207 patients with hyperthyroidism and atrial fibrillation were older than 45 years (Ernstene, 1938) and atrial fibrillation was found to be related with the duration of existence of hyperthyroidism (Willius, Boothby and Wilson, 1923).

Other authors (Kulbertus, 1973) could not confirm this concept. However, some evidence that atrial fibrillation is not caused by hyperthyroidism itself but, more likely, is induced by the excess of thyroid hormones and maintained only in the presence of different kinds and degrees of cardiovascular damage, is given by the following facts.

(1) Chronic atrial fibrillation associated with hyperthyroidism occurs only in patients of over 40 years of age while atrial fibrillation in the younger patients remains paroxysmal (Boone, 1945).

(2) Only 20–25% of all hyperthyroid patients develop chronic atrial fibrillation (Ernstene, 1938; Jervell, 1952; Sandler and Wilson, 1959; Rohrbach, 1968; Bourel *et al.*, 1969).

(3) Onset and spontaneous conversion of atrial fibrillation does not correspond to onset and correction of hyperthyroidism (Willius *et al.*, 1923; Symons, Richardson and Wood, 1971).

(4) Not all efficiently treated hyperthyroid patients with atrial fibrillation subsequently spontaneously regain sinus rhythm (Ernstene, 1938; Silver *et al.*, 1962; Bock and Klein, 1972).

(5) Atrial fibrillation can be converted to sinus

rhythm and the latter can be maintained with antiarrhythmic drugs during hyperthyroidism, independently of the antithyroid treatment or thyroid function present (Levi and Proto, 1972; De Vil and Bruyneel, 1974).

(6) Hyperthyroidism does not only trigger off atrial fibrillation but has been found to induce all kinds of dysrhythmias and conduction disturbances in patients of over 40 years of age depending on concomitant pathophysiological conditions (Cookson, 1959; Fairhurst and Sash, 1959; Lyngborg and Jacobsen, 1972).

Therefore, there is no need to leave the hyperthyroid patient, with his disturbing symptoms of palpitations or atrial fibrillation with fast ventricular rate and decreased cardiac output and effort tolerance (Benchimol, Lowe and Akre, 1965; Bouma and May, 1967), until stable euthyroid state is obtained and hoping atrial fibrillation will spontaneously convert to sinus rhythm. Although propranolol (Howitt and Rowlands, 1966), guanethidine (Lee, Bronsky and Waldstein, 1962; Waldstein *et al.*, 1964; Goldstein and Killip, 1965) and reserpine (Canary *et al.*, 1957) have been shown to diminish palpitations in patients with hyperthyroidism, they do not convert atrial fibrillation to sinus rhythm, and a complete return to normal conditions of heart rate and cardiac output is not achieved. Propranolol (Howitt and Rowlands, 1967) and guanethidine (Goldstein and Killip, 1965) should be used with caution in hyperthyroidism since both drugs reduce blood flow to certain vascular beds out of proportion to the oxygen demand. Another alternative is offered by lidoflazine therapy. This original compound prolongs reactive hyperaemia in mini pigs after coronary artery occlusion (Jageneau, Schaper and Van Gerven, 1969), reduces consumption of nitroglycerine tablets and improves exercise tolerance in patients with coronary heart disease (Batlouni, Bertolami and Duprat, 1968; Bernstein and Peretz, 1972; Piessens and De Geest, 1972). Lidoflazine converts atrial fibrillation to sinus rhythm in 70–80% of the patients suitable for cardioversion and the therapy compares favourably with quinidine-induced conversions (De Vil and Bruyneel, 1974).

The rate of pacemaker activity and depolarization (dV/dt) and amplitude of the action potential and conduction velocity of *in vitro* cardiac muscle preparations are reduced by lidoflazine. The duration of the action potential and of the effective refractory period is prolonged (Carmeliet and Xhonneux, 1971). Lidoflazine may thus be compared to local anaesthetics and other antiarrhythmic drugs, such as quinidine. It has no obvious chronotropic (Keulen, 1973) or inotropic (Bruyneel, personal observation) effect in the resting state. Lidoflazine is not known to interfere with the thyroid hormone metabolism or

any of its diagnostic tests. Bernstein and Peretz (1972) found QT_c to be prolonged in their patients with lidoflazine. Keulen (1973) found the QT_c unchanged. Increased incidence of ventricular dysrhythmias has been reported during lidoflazine treatment in patients with atrial fibrillation and overt heart failure, enlarged heart size or conditions where decreased body potassium can be expected (Piessens *et al.*, 1970; Schlepper and Derro, 1972). This was not the experience when classic selection criteria for cardioversion were applied (De Vil and Bruyneel, 1974).

The advantages of lidoflazine therapy seem to be the absence of side effects and drug interference and the low dosage needed to maintain sinus rhythm with excellent results after cardioversion. Batlouni (unpublished report) found twenty-eight of thirty patients with atrial fibrillation to be still in sinus rhythm 1 year after having been converted to sinus rhythm with lidoflazine. Twenty-four patients had taken one tablet daily for 1 year as maintenance therapy. Our limited experience with lidoflazine in hyperthyroid patients with atrial fibrillation accords with previous observations as concerns its efficacy to convert atrial fibrillation to sinus rhythm and its maintenance. It confirms the intrinsic anti-arrhythmic effect of lidoflazine which is obvious within a few days or weeks in contrast to its anti-anginal effect which starts after 2–3 months of therapy.

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