Pharmacokinetics and dromotropic activity of ajmaline in rats with hyperthyroidism

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- 1 The pharmacokinetics and the dromotropic action (increased PQ interval) of intravenously administered ajmaline (2 mg kg^{-1}) were studied in hyperthyroid rats with sinus tachycardia. The hyperthyroidism was induced by intraperitoneal injection of 3,5,3'-triiodo-L-thyronine (0.5 mg kg^{-1}) for 4 days.
- 2 The change in the ajmaline concentration in whole blood could be described by a biexponential equation. The steady state distribution volume of ajmaline decreased from 4.81 l kg^{-1} in control rats to 3.80 l kg^{-1} in hyperthyroid rats and the total body blood clearance was slightly higher in hyperthyroid rats than in control rats.
- 3 Ajmaline exhibited a saturable binding to rat plasma proteins, and one kind of binding site was found in the observed range of concentrations. The binding capacity was 2 fold higher in hyperthyroid rats than in control rats.
- 4 On the basis of the plasma unbound concentration, ajmaline exhibited an increased negative dromotropic activity in hyperthyroid rats compared with control rats.
- 5 A positive correlation was found between the pacing rate and the dromotropic action of ajmaline on atrioventricular conduction in isolated perfused hearts. There was no significant difference in the rate-dependence of the effect of ajmaline on the heart between control and hyperthyroid rats.
- 6 Our findings suggest that the increased dromotropic activity of ajmaline is mainly due to the increased heart rate in hyperthyroid rats.

Introduction

Most antiarrhythmic drugs have a relatively low therapeutic index and often produce intolerable side effects. Variability in the patients response to antiarrhythmics is a crucial consideration in designing dosage regimens, and the definition of the mechanisms of interindividual variability in drug response is of critical importance (Myerburg *et al.*, 1981; Follath *et al.*, 1983; Vozeh *et al.*, 1987).

Altered thyroid function may cause a significant variation in both the pharmacokinetics and the pharmacodynamics of antiarrhythmics, because thyroid hormones have an effect on fundamental molecular processes resulting in alteration of many physiological functions. Thyroid dysfunction affects the disposition of many drugs including propranolol

and digoxin (Shenfield, 1981). Tachycardia is a common symptom associated with hyperthyroidism and may affect the antiarrhythmic activity of Class I drugs, because these drugs have been shown to depress the maximal upstroke velocity during phase 0 of the cardiac action potential in a frequency-dependent fashion (Heistracher, 1971; Hondeghem & Katzung, 1977). In addition, sudden cardiac death, ventricular arrhythmias, heart block and myocardial infarction may occur during thyrotoxicosis (Wei *et al.*, 1979).

This background prompted us to investigate the effects of thyroid dysfunction on the pharmacokinetics and the pharmacodynamics of an antiarrhythmic drug, by means of hyperthyroid model rats with sinus tachycardia. As a model drug, we selected a Class I antiarrhythmic drug ajmaline, the

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dromotropic action of which on atrioventricular conduction can be assessed by measuring PQ intervals on the electrocardiogram in rats (Hashimoto *et al.*, 1986). Because the pharmacological effects of ajmaline have been shown to be affected by plasma protein binding (Yasuhara *et al.*, 1987), the dromotropic activity in hyperthyroid rats was determined from the plasma unbound concentration. Furthermore, in rat isolated perfused hearts, we examined whether the change in the heart rate could affect the dromotropic activity of ajmaline, and to what extent the variations of the dromotropic activity of ajmaline in thyroid dysfunction could be accounted for by the frequency-dependent nature of the drug's action.

Methods

Induction of hyperthyroidism in rats

Male Wistar rats, each weighing 310–390 g, were used. Hyperthyroid (T_3) rats were produced by daily intraperitoneal injections of 3,5,3'-triiodo-L-thyronine (Sigma) 0.5 mg kg^{-1} in a solution volume of 1 ml kg^{-1} for 4 days (Gross & Lues, 1985). Animals that received the vehicle alone (4 mM NaOH in isotonic saline) served as a control. The experiments were begun 15 h after the last treatment.

Pharmacokinetics and pharmacological effect of ajmaline

The rats were anaesthetized with 50 mg kg^{-1} sodium pentobarbitone, administered as required. A catheter in the femoral artery was used for blood sampling and for measuring systemic arterial blood pressure by means of a capacitance transducer (Toyo Baldwin MPU-0.5-290-0-III). Another catheter was placed in the femoral vein for drug administration. The electrocardiogram (ECG) was recorded with bipolar standard limb leads. Arterial blood pressure, ECG and heart rate were monitored continuously by use of a polygraph (San-ei Model 366) and a recorder (San-ei Model 8K21-L). Body temperature was maintained with appropriate heating lamps.

Ajmaline (Gilurytmal, Nippon Chemiphar, 25 mg ml^{-1}) was diluted with isotonic saline, and 2 mg kg^{-1} was administered intravenously as a bolus injection of 1 ml kg^{-1} . Heparinized blood samples (0.15 ml) for the assay of ajmaline in whole blood were collected at 2, 5, 10, 30, 60, 90 and 120 min after the ajmaline injection. From the ECG recordings run at a paper speed of 250 mm s^{-1} , the PQ interval was measured before and after the injection of ajmaline, and the percentage increase of the PQ interval was calculated for measurement of the dromotropic action of the drug.

Plasma protein binding and erythrocyte partitioning of ajmaline

To calculate the plasma unbound concentration (Pf) from the whole blood concentration (Cb), the plasma protein binding and erythrocyte partitioning of ajmaline were determined *in vitro*. The heparinized blood was collected from four rats per group. Ajmaline was added to the blood to yield Cb from 0.1 to $1.0 \mu\text{g ml}^{-1}$. After incubation for 15 min at 37°C , the haematocrit value (Ht) was measured by a Kubota Model KH-120 Hematocrit System ($10,000 \text{ r.p.m.}$, 5 min). After the plasma was separated by centrifugation, 0.1 ml of the plasma sample was taken for determination of the ajmaline concentration in plasma (Cp). Binding of ajmaline to plasma proteins was measured by the ultrafiltration technique by use of a Micropartition System (Amicon MPS-1). A 0.8 ml sample of plasma was placed in the ultrafiltration device equipped with a YMB membrane (Amicon) and centrifuged at $2000g$ for 15 min at 20°C . About $80 \mu\text{l}$ of the ultrafiltrate was obtained for the determination of Pf. No significant adsorption of ajmaline was observed onto the ultrafiltration device (Yasuhara *et al.*, 1987).

Heart perfusion study

To analyse the dromotropic action of ajmaline in detail, the isolated perfused heart of the rat was subjected to artificial pacing. The anaesthetized rats were heparinized with 1000 iu kg^{-1} of sodium heparin. The rat isolated heart was perfused in a retrograde manner by the Langendorff technique in a non-recirculating fashion (Carmeliet & Zaman, 1979). Standard Krebs-Henseleit solution containing 11.1 mM D-glucose, aerated with $95\% \text{ O}_2 + 5\% \text{ CO}_2$ and maintained at 31°C was used for the perfusion under a pressure of 130 mmHg . The hearts were stimulated *via* two stainless wire electrodes placed on the upper surface of the right auricle at 4 V and 1 ms duration, by means of an electronic stimulator (San-ei Model 3F46) and an isolator (San-ei Model 5361). Two steel wire electrodes fixed to the stainless steel aortic cannula and the apex of the ventricle were used to record the ECG. At any pacing rate, the ECG was equilibrated within 30 pacing stimuli, whether ajmaline was present or not. The equilibrated atrioventricular (AV) intervals at each pacing rate were measured before and after 30 min of the perfusion with ajmaline $0.326 \mu\text{g ml}^{-1}$, and the percentage increase of the AV interval was calculated.

Assay of ajmaline

A specific reverse phase high performance liquid chromatographic (h.p.l.c.) method described pre-

Table 1 Comparison of the characteristics between 3,5,3'-triiodo-L-thyronine-treated (T_3) rats and control rats

	Control (n = 4)	T_3 (n = 5)
Body weight		
before treatment (g)	345 $\pm$ 7	336 $\pm$ 7
after 4 days treatment (g)	353 $\pm$ 6	316 $\pm$ 9**
gain (g)	8 $\pm$ 6	-20 $\pm$ 4***
Heart weight (g kg ⁻¹)	3.06 $\pm$ 0.14	4.20 $\pm$ 0.11†
Haemodynamics		
heart rate (min ⁻¹)	374 $\pm$ 21	537 $\pm$ 17†
mean blood pressure (mmHg)	133 $\pm$ 9	132 $\pm$ 5
PQ interval (ms)	39.3 $\pm$ 0.8	35.9 $\pm$ 1.2

Values are expressed as mean $\pm$ s.e.mean for n animals.

** $P < 0.025$; *** $P < 0.01$ and † $P < 0.005$.

viously (Hori *et al.*, 1984) was used to quantitate ajmaline. The assay for Cb and Cp involved extraction of 0.1 ml sample and 1.0 ml glycine buffer (pH 10.0, 0.1 M, saturated with sodium chloride) with 5 ml of diethylether, and re-extraction of the organic phase with 0.2 ml of 0.85% phosphoric acid solution. A 50 μ l sample of the water phase or the ultrafiltrate for the determination of Pf was subjected to h.p.l.c.

Data analysis

The disposition of ajmaline after intravenous administration was analysed by a biexponential equation: $Cb(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$ for Cb at time t

Figure 1 Time course of ajmaline concentration in whole blood in T_3 (●, $n = 5$) and control (○, $n = 4$) rats following i.v. injection of ajmaline 2 mg kg⁻¹. The vertical bar represents s.e.mean.

** $P < 0.025$ and † $P < 0.005$.

(Hashimoto *et al.*, 1986). The total body blood clearance (Cl_t) and the steady state distribution volume (Vd_{ss}) were calculated by the following equation: $Cl_t = \text{dose}/(A/\alpha + B/\beta)$ and $Vd_{ss} = Cl_t^2(A/\alpha^2 + B/\beta^2)/\text{dose}$ (Gibaldi & Perrier, 1982).

The plasma protein binding of ajmaline was analysed by the following equation, assuming one class of binding site in plasma: $Cp = Pf + N \cdot K \cdot Pf / (1 + K \cdot Pf)$, where N and K are the maximal binding capacity and association constant, respectively. The erythrocyte partitioning of ajmaline was studied by analysing the relationship of Pf to the drug concentration in blood cells (Cr), which was derived from the equation: $Cr = \{Cb - Cp(1 - Ht)\}/Ht$. Assuming a Freundlich type equation (Martin *et al.*, 1969), Cr was related to Pf in the following equation: $Cr = a \cdot Pf^b$, where a and b are constants. Accordingly, Pf could be estimated from any Cb by an iterative method after the values of N , K , a , b and Ht were determined (Yasuhara *et al.*, 1987).

The parameters were determined by least squares regression analysis using a digital computer. Values are expressed as mean $\pm$ s.e.mean. Statistical significance of difference between mean values was calculated by a non-paired t test provided that the variances were similar. If this was not the case, Mann-Whitney's U-test was applied. P values of less than 0.05 (two-tailed) were considered to be significantly different.

Results

Table 1 shows the effects of 3,5,3'-triiodo-L-thyronine-induced hyperthyroidism on various characteristics of rats. The body weight of the animals decreased slightly after 4 days of treatment with 3,5,3'-triiodo-L-thyronine. The heart weight normalized by the body weight was significantly higher in T_3 rats than in control rats. The heart rate determined under pentobarbitone anaesthesia was significantly

Table 2 Pharmacokinetic parameters of ajmaline at an intravenous dose of 2 mg kg^{-1} in hyperthyroid (T_3) and control rats

	Control ($n = 4$)	T_3 ($n = 5$)
A ($\mu\text{g ml}^{-1}$)	1.32 ± 0.12	1.31 ± 0.07
B ($\mu\text{g ml}^{-1}$)	0.245 ± 0.008	$0.302 \pm 0.013^{**}$
α (min^{-1})	0.280 ± 0.013	0.279 ± 0.008
β (min^{-1})	0.0165 ± 0.0005	$0.0222 \pm 0.0011^\dagger$
Cl_t ($\text{ml min}^{-1} \text{ kg}^{-1}$)	102 ± 1	$109 \pm 2^{**}$
Vd_{ss} (l kg^{-1})	4.81 ± 0.07	$3.80 \pm 0.25^{***}$

Parameters were calculated from the biexponential equation by non-linear iterative least squares method using a digital computer. A and B are the extrapolated intercepts on time zero, and α and β are the rapid and slow disposition rate constant, respectively. Cl_t is the total body blood clearance and Vd_{ss} is the steady state distribution volume. Values are expressed as mean $\pm$ s.e.mean for n animals.

$^{**}P < 0.025$; $^{***}P < 0.01$ and $^\dagger P < 0.005$.

higher in T_3 rats than in control rats, but the mean arterial blood pressure was similar in the two groups of rats. There was no significant difference in the PQ interval between T_3 and control rats.

Figure 1 shows the blood concentrations of ajmaline following i.v. injection (2 mg kg^{-1}) in T_3 and control rats. Cb values in T_3 rats were significantly lower than those in control rats at 90 and 120 min after the dosing. Cb data were fitted to the biexponential equation, and Table 2 shows the estimated pharmacokinetic parameters. B, β and Cl_t were slightly increased, and Vd_{ss} was decreased in T_3 rats compared with the control rats.

In T_3 and control rats the heart rate transiently decreased just after the administration of ajmaline (2 mg kg^{-1}); the heart rate in T_3 rats was higher than that in control rats throughout the experiments (Figure 2). The mean arterial blood pressure was not affected by i.v. administration of ajmaline (2 mg kg^{-1}) in either T_3 or control rats, and its change at 2 min after dosing was $3 \pm 4\text{ mmHg}$ ($n = 5$) and $-5 \pm 3\text{ mmHg}$ ($n = 4$) in T_3 and control rats, respectively. Following injection of ajmaline (2 mg kg^{-1}), both T_3 and control rats showed rapid prolongation of PQ intervals, and the percentage increases of the PQ interval at 2 min after dosing were $43.7 \pm 3.9\%$ ($n = 5$) in T_3 rats and were significantly ($P < 0.025$) greater than the values of $34.2 \pm 1.3\%$ ($n = 4$) in control rats. Thereafter, the PQ interval decreased gradually and returned to the pre-dose levels by 120 min.

To determine the pharmacological effect of ajmaline from the unbound drug concentration in blood, the relationship of Pf to Cb in T_3 and control rats was studied in four separate experiments (Figure 3).

Figure 2 Time course of heart rate in T_3 ($\bullet$, $n = 5$) and control ($\circ$, $n = 4$) rats after the i.v. injection of ajmaline 2 mg kg^{-1} . The vertical bar represents s.e.mean.

Pf was significantly lower in T_3 rats than in control rats, over the concentration-range studied. The plasma protein binding and erythrocyte partitioning of ajmaline were also measured in order to describe the relationship of Pf to Cb quantitatively. As shown in Table 3, the decreased unbound fraction of ajmaline in the blood of T_3 rats was mainly due to the increased binding capacities of T_3 rat plasma. The simulated curves in Figure 3, which were drawn to fit the mean values of plasma protein binding parameters, erythrocyte partitioning parameters and haematocrit value in each group, were highly correlated with the observed data.

The effect of hyperthyroidism on the negative dromotropic activity of ajmaline was assessed by

Figure 3 Relationship between whole blood and plasma unbound concentration of ajmaline in T_3 ($\bullet$, $n = 4$) and control ($\circ$, $n = 4$) blood. The vertical bar represents s.e.mean. The solid curves were drawn to fit the mean parameters in each group, as given in Table 1.

$^*P < 0.05$; $^{**}P < 0.025$ and $^{***}P < 0.01$.

Table 3 Protein binding and erythrocyte partitioning parameters of ajmaline in hyperthyroid (T_3) and control rats

	Control ($n = 4$)	T_3 ($n = 4$)
N ($\mu\text{g ml}^{-1}$)	1.72 ± 0.23	$3.48 \pm 0.61^*$
K ($\text{ml } \mu\text{g}^{-1}$)	2.40 ± 0.08	2.45 ± 0.23
a	2.79 ± 0.17	$2.12 \pm 0.06^{***}$
b	1.05 ± 0.06	1.05 ± 0.05
Ht	0.414 ± 0.009	$0.438 \pm 0.003^*$

The drug concentration data in plasma for individual experiments were fitted to the equation $C_p = P_f + N \cdot K \cdot P_f / (1 + K \cdot P_f)$ for the plasma concentration, C_p at the plasma unbound concentration, P_f . The blood cell concentrations (Cr) were analysed by the following equation: $Cr = a \cdot P_f^b$. Ht is the haematocrit value. Values are expressed as mean $\pm$ s.e.mean for n experiments.

* $P < 0.05$ and *** $P < 0.01$.

analysing the relationship of the percentage increase of the PQ interval to P_f . Figure 4 shows the response to P_f on a semi-logarithmic scale, indicating the difference in the negative dromotropic activity between the two groups of rats. In fact, the relationship between P_f -response could be analysed by linear regression in individual rats ($P < 0.005$). The slopes were $197.5 \pm 31.6\% \text{ ml } \mu\text{g}^{-1}$ ($n = 5$) in T_3 rats, and were significantly greater than the values of $110.4 \pm 8.9\% \text{ ml } \mu\text{g}^{-1}$ ($n = 4$) in control rats ($P < 0.025$). The intercepts were very small: $0.9 \pm 0.2\%$ and $0.0 \pm 0.5\%$ in T_3 and control rats, respectively. These results indicated the increase in

Figure 4 Relationship between plasma unbound concentration and PQ interval change in T_3 (●, $n = 5$) and control (○, $n = 4$) rats following i.v. injection of ajmaline 2 mg kg^{-1} . The vertical bars represent s.e.mean. The solid curves were drawn by the following equations: $R = 110.4 P_f$ for control rats and $R = 197.5 P_f + 0.9$ for T_3 rats, where R is response and P_f is the plasma unbound concentration.

Table 4 Rate-dependent dromotropic activity of ajmaline ($1 \mu\text{M}$, $0.326 \mu\text{g ml}^{-1}$) for atrioventricular (AV) conduction in isolated hyperthyroid (T_3) and control rat hearts

Pacing rate (min^{-1})	Change in AV interval (% increase)	
	Control ($n = 5$)	T_3 ($n = 5$)
150	16	
200	20, 22	
250	25 ± 1	25 ± 1
300	28 ± 1	28 ± 1
350	32 ± 2	31 ± 2
400	34	35 ± 2
450		33, 40

Values are expressed as mean $\pm$ s.e.mean for n hearts. If this is not the case, individual values are quoted.

the negative dromotropic activity of ajmaline in T_3 rats compared with control rats.

The mechanism of the increased dromotropic activity of ajmaline in hyperthyroidism was investigated by means of isolated perfused rat hearts. The AV intervals in isolated heart preparations in the absence of ajmaline were similar in T_3 and control rats: $65.0 \pm 2.5 \text{ ms}$ and $62.2 \pm 1.5 \text{ ms}$ at the pacing rate of 250 min^{-1} , and $71.8 \pm 3.5 \text{ ms}$ and $69.8 \pm 2.5 \text{ ms}$ at the pacing rate of 350 min^{-1} in T_3 ($n = 5$) and control ($n = 5$) rats, respectively. Ajmaline ($0.326 \mu\text{g ml}^{-1}$) produced a rate-dependent dromotropic effect over the range of the pacing rate, to which the perfused heart could respond; 250 – 450 min^{-1} and 150 – 400 min^{-1} in T_3 and control rat hearts, respectively. Table 4 shows the percentage increases of the AV interval for each pacing rate in T_3 and control hearts. The relationship between the pacing rate and the percentage increase of the AV interval could be analysed by the linear regression for individual rat hearts ($P < 0.05$). The slope was $0.070 \pm 0.010\% \text{ min}$ and $0.080 \pm 0.009\% \text{ min}$, and the intercept was $6.8 \pm 2.6\%$ and $4.3 \pm 2.1\%$ in T_3 ($n = 5$) and control ($n = 5$) rat hearts, respectively. Thus, there was no significant difference in the rate-dependence of the ajmaline effect between hearts obtained from T_3 and control rats. These results suggested that the increased dromotropic activity of ajmaline was mainly due to the increased heart rate associated with the hyperthyroidism.

Discussion

The present study demonstrated that hyperthyroidism could affect both the pharmacokinetics and the pharmacodynamics of ajmaline. Thyroid hormones are said to have an effect on fundamental molecular processes resulting in alteration of many

physiological functions including cardiac output, blood flow rate in tissues and metabolic activity in the liver (Shenfield, 1981). In the present study T_3 rats had sinus tachycardia and cardiac hypertrophy, which suggested accelerated heart function.

T_3 rats had smaller V_{dss} and slightly higher Cl_t of ajmaline than the control rats. The plasma protein binding of ajmaline *in vitro* was increased for T_3 rats compared with control rats. It has been suggested that drug distribution in the body depends on plasma protein binding, and increased binding can lead to a decrease in the distribution volume of the drug which can be distributed to the tissues (Tozer, 1981). Accordingly, the smaller distribution volume in T_3 rats is likely to be due to the lower unbound fraction of ajmaline in the blood. On the other hand, the total clearance of ajmaline was increased in T_3 rats in spite of the lower unbound fraction. This was probably related to the mechanism of ajmaline clearance. Ajmaline is poorly excreted in the urine (Kleinsorge & Gaida, 1961; Iven, 1977) and avidly extracted by the liver (Yamada *et al.*, 1986). Moreover, we have shown that the total clearance of ajmaline is decreased in rats with acute myocardial ischaemia compared with sham-operated control rats (Hashimoto *et al.*, 1986). These findings suggested that the elimination process of ajmaline is not much restricted either by the unbound fraction in the blood or by the metabolic activity in the liver, but is largely dependent on the hepatic blood flow rate (Wilkinson & Shand, 1975). Accordingly, the principal cause for the increased total blood clearance in T_3 rats may be the increased hepatic blood flow rate in hyperthyroidism (Wells *et al.*, 1983).

In the present study, the capacity of plasma protein binding of ajmaline, a weak basic drug with a pK_a of 8.3 (Petter, 1974), was increased in T_3 rats compared with control rats. We do not have a clear explanation for the mechanism of this increased binding. The effect of hyperthyroidism on the plasma protein binding of propranolol, another basic drug, has been studied by several groups, but the results are controversial. Feely *et al.* (1981) have reported that the protein binding of propranolol is lower in hyperthyroidism than in the euthyroid state, and

have implied the possibility of hyperthyroidism-induced changes in the concentration of albumin or α_1 -acid glycoprotein, and the presence of binding displacement in the plasma of hyperthyroid patients. On the contrary, Wells *et al.* (1983) have reported that the plasma unbound fraction of propranolol is slightly lower in thyrotoxic patients than in euthyroid patients although not significantly.

We have shown that the negative dromotropic action of ajmaline for the AV conduction system can be quantitatively assessed by measuring the PQ interval in rats (Hashimoto *et al.*, 1986) and dogs (Yasuhara *et al.*, 1987). On the other hand, changes in the extent of the plasma protein binding have been shown to affect the responses of some anti-arrhythmic drugs, including lignocaine (Rick *et al.*, 1987) and disopyramide (Huang & Øie, 1982). We have also shown that the dromotropic action of ajmaline correlates with unbound drug concentrations better than with total plasma concentrations in dogs (Yasuhara *et al.*, 1987). Accordingly, in the present study, we determined the dromotropic activity of ajmaline from the unbound drug concentrations, and found it to be significantly increased in T_3 rats.

The isolated heart perfusion study showed that ajmaline could decrease the AV conduction rate in a frequency-dependent fashion (Table 4). A positive linear correlation was observed between the pacing rate and the prolongation of the AV interval by ajmaline, and there was no difference in the pacing rate-dependence between control and T_3 rats. This indicated that both groups of rats had similar cardiac sensitivity to the dromotropic action of ajmaline at the same heart rate. Since T_3 rats had a much higher heart rate than the control rats, ajmaline could produce a higher dromotropic effect in T_3 rats than in the control rats at the same unbound drug concentration in the blood.

In conclusion, these results suggest that hyperthyroidism has pronounced effects on both the pharmacokinetics and pharmacodynamics of ajmaline, and that the heart rate is an important determining factor for the negative dromotropic effect of ajmaline.

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