Br. J. Pharmac. (1983), **79**, 167–175

Electrophysiological effects of imipramine in non-treated and in imipramine-pretreated rat atrial fibres

J. Manzanares & J. Tamargo

Department of Pharmacology, School of Medicine, Universidad Complutense, Madrid-3, Spain

1 The effect of imipramine (Imip) in concentrations between 10^{-7} M and 5×10^{-5} M has been studied on rat atrial transmembrane potentials. In another group of experiments the effect of Imip was studied in atrial fibres from rats pretreated for 24 days with twice daily intraperitoneal injections of Imip 7.5 mg/kg or saline.

2 In non-treated atria Imip depressed action potential amplitude and *Vmax*, reduced the resting membrane potential and shifted the membrane responsiveness and recovery time curves downward and to the right.

3 Imip also prolonged the action potential duration and the effective refractory period, lengthening the effective refractory period relative to action potential duration.

4 Pretreatment with Imip decreased the resting membrane potential, amplitude and *Vmax* of the action potential and prolonged the effective refractory period. Further addition of Imip produced similar but more marked changes than in non-treated animals.

5 Imip suppressed the spontaneous atrial automaticity as well as the abnormal automaticity induced by $BaCl_2$, aconitine, ouabain or isoprenaline.

6 The drug produced a negative inotropic effect and depressed the amplitude of the slow contractions elicited by isoprenaline in K-depolarized atria.

7 It is concluded that even when the effects of Imip are similar to those of quinidine (group I of antiarrythmics), it also produces a reduction in Ca and K conductances.

Introduction

The electrophysiological effects of imipramine (Imip) have been studied in rat (Auclair, Guida & Lechat, 1969) and guinea-pig ventricular muscle (Garcia de Jalón, Rodriguez & Tamargo, 1978) and in canine (Rawling & Fozzard, 1979; Weld & Bigger, 1980; Brennan, 1980) and bovine (Rodriguez & Tamargo, 1980) Purkinje fibres. All these studies have demonstrated that Imip reduced amplitude, *Vmax* and conduction velocity of the action potential and depressed membrane responsiveness in ventricular fibres. Moreover, Imip also suppressed the slow action potentials induced by isoprenaline in ventricular muscle fibres (Garcia de Jalón *et al.*, 1978). Despite all these studies, there is little information concerning the effects of Imip on atrial fibres. Matsuo (1967) found that at low concentrations (0.1 μg/ml), Imip did not alter the action potential configuration or the spontaneous sinus rate of rabbit isolated atria, whereas at higher concentrations, corresponding to clinically toxic plasma levels, Imip also reduced *Vmax* and conduction velocity with little change in action potential configuration.

On the other hand, it is well known that some effects of tricyclic antidepressant drugs appear only after days or weeks of treatment and, to our knowledge, the electrophysiological effects of chronic treatment with tricyclic antidepressants have not been previously studied on cardiac fibres.

The present work was, therefore, undertaken to study the electrophysiological effects of a wide range of concentrations of Imip in rat isolated atria obtained from control animals and in atria obtained from rats treated for 24 days with Imip.

Methods

Sprague-Dawley rats (200–250 g) were killed by a blow on the head and the hearts rapidly removed. Right and left atria were dissected and placed in a 10 ml organ bath containing Tyrode solution as described previously (Tamargo, 1980). Right atria were allowed to beat spontaneously and left atria were stimulated regularly at a basal rate of 3 Hz through

bipolar platinum electrodes by square wave pulses (1 ms duration, twice threshold strength). The frequency and amplitude of contractions were recorded isometrically by means of a Grass FT03 force-displacement transducer on a Grass polygraph. Resting tension was adjusted to 1.0 g and a 30 min equilibration period was allowed before control measurements were made. The techniques used and definitions of the sinus node recovery time and slow contractions are as previously described (Tamargo, De Miguel & Tejerina, 1982).

Intracellular recordings

Spontaneously beating right atria and driven left atria were pinned to the bottom of a 10 ml Lucite chamber and superfused with Tyrode solution gassed with 95% O_2:5% CO_2 at 32°C. Transmembrane potentials were recorded through glass microelectrodes filled with 3 M KCl having resistances of 10–30 megohms, displayed via high-impedance, capacity neutralizing amplifiers (WPI) and photographed on film (Rodriguez & Tamargo, 1980). Transmembrane action potential parameters measured included: action potential amplitude, maximum rate of depolarization (*Vmax*) and action potential duration measured to 50% (APD_{50}) and 90% (APD_{90}) repolarization. The relationship between *Vmax* and the resting membrane potential, i.e. membrane responsiveness, was measured by stimulation in different K concentrations (2.7 to 13.4 mM; Rodriguez & Tamargo, 1980). The effective refractory period (ERP) and the recovery time were measured by introducing premature test-stimuli with an intensity of twice the basic stimulus and 2 ms duration, at different time intervals after the preceding basic action potential. The interpolation and shift along the voltage axis was carried out after every eight basic stimuli.

Spontaneous activity was induced in right atria by adding $BaCl_2$ (0.2 mM), ouabain (5×10^{-7} M), aconitine (10^{-6} M) and isoprenaline (10^{-6} M) to the normal Tyrode solution. Atria were allowed to attain stable spontaneous rhythms before adding increasing concentrations of Imip to the perfusate.

Experiments in imipramine pretreated animals

In further studies, rats (200–250 g) were injected with Imip (7.5 mg/kg twice daily i.p.) or saline (1 ml/kg) for 24 days. The animals were killed 12–16 h after the final injection and both right and left atria were set up for measurement of rate and amplitude of contractions and for the recording of transmembrane action potentials as described above.

Drugs

Imipramine hydrochloride (Ciba-Geigy) was dissolved in distilled deionized water. Further dilutions were carried out in Tyrode solution to obtain final concentrations between 10^{-7} M and 5×10^{-5} M equivalent to 0.032 and 16.0 ng/ml, respectively. Other drugs used were isoprenaline hydrochloride (Sigma), $BaCl_2$ (Merck), aconitine (Sigma) and ouabain octahydrate (Sigma).

Throughout the paper, results are expressed as mean ± s.e.mean. Statistical significance was determined by Student's *t* test and differences were considered significant when $P < 0.05$.

Results

Electrophysiological effects of imipramine on atrial fibres

The effects of Imip in concentrations between 10^{-7} M and 5×10^{-5} M were studied in 12 atria. The effects of the drug were usually apparent within 5 min and stabilized within 30 min. Control values of the meas-

Table 1 Electrophysiological effects of imipramine on rat atrial fibres

Drug concentration (M)	*Resting potential* (mV)	*Amplitude* (ms)	*Vmax* (V/s)	APD_{50} (ms)	APD_{90} (ms)	*ERP* (ms)
0 (14)	82.3 ± 0.4	105.7 ± 1.1	88.9 ± 8.9	11.5 ± 1.3	32.1 ± 3.6	27.3 ± 1.3
10^{-7} (14)	82.3 ± 0.5	105.8 ± 1.6	70.1 ± 6.7*	15.2 ± 2.0*	44.5 ± 6.0*	40.8 ± 2.8*
10^{-6} (14)	82.0 ± 0.8	103.1 ± 1.9*	61.2 ± 5.6**	16.9 ± 2.7**	50.2 ± 7.4**	54.9 ± 5.0***
10^{-5} (12)	81.3 ± 1.2**	96.0 ± 1.6***	40.5 ± 5.3***	18.4 ± 2.7**	54.0 ± 7.1**	90.6 ± 10.5***
2.5×10^{-5} (12)	75.2 ± 1.8***	74.6 ± 2.8***	21.5 ± 2.8***	27.8 ± 4.2***	73.5 ± 9.6***	112.8 ± 66.9***

Values are mean ± s.e.mean. Number of observations (*n*) in parentheses. Readings started after 30 min of perfusion with imipramine. APD_{50} and APD_{90} refer to action potential duration measured to 50% and 90% repolarization, repectively.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

ured parameters and values obtained after 30 min exposure to different concentrations of Imip are shown in Table 1. Records from a typical experiment are shown in Figure 1. With the lowest concentration, 10^{-7} M, a slight decrease in the *Vmax* and a prolongation of the APD were noted. At 10^{-6} M these changes were exaggerated and the action potential amplitude was decreased as well. With 10^{-5} M, the resting membrane potential was decreased and thus a further reduction in action potential amplitude and *Vmax* was observed. At 2.5×10^{-5} M, the reduction of the resting membrane potential and *Vmax* was accompanied by different degrees of conduction block between the stimulating and the recording electrode sites. In fact, after 30 min in this concentration the upstroke of the action potential frequently consisted of two phases: a first phase markedly reduced in rate and amplitude followed by a low rising secondary depolarization up to the normal plateau level (Figure 1e). At 5×10^{-5} M the resting membrane potential was decreased to -71.2 ± 1.8 mV and all fibres became inexcitable within 15 min. Imip also produced significant changes in the repolarization time course of the action potential. In the presence of Imip the slope of phases 2 and 3 decreased and the duration of phase 3 increased which led to a concentration-dependent prolongation in the APD at both 50% and 90% levels of repolarization.

The effects produced by concentrations of Imip up to 10^{-5} M were reversible within 60 min of perfusion, with control Tyrode solution. At higher concentrations the effects of Imip were only partly reversed during the washout.

Effect of imipramine on membrane responsiveness and recovery time

The effect of Imip on the relation between *Vmax* and membrane potential at the onset of depolarization (i.e. membrane responsiveness) was studied in 6 left atria by recording the electrical activity during a stepwise increase of the external K concentration. As is shown in Figure 2, Imip, 5×10^{-6} M and 10^{-5} M, depressed the upper and flat portions more than the steep portion of the S-shaped curve and, therefore, shifted the curve along the voltage axis to more hyperpolarized potentials. At 10^{-5} M the maximum value for *Vmax* at the normal resting potential was markedly reduced and the membrane potential for which *Vmax* is reduced to half of its maximal value,

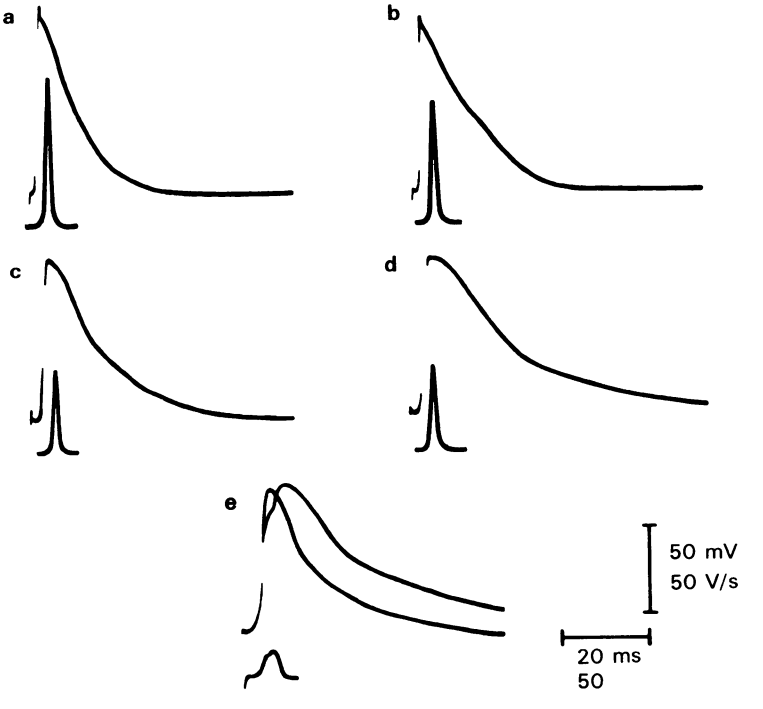

Figure 1 Effects of increasing concentrations of imipramine (Imip) on transmembrane action potentials from a rat atrial fibre. The upper trace in each panel represents the transmembrane potential and the lower trace the maximum rate of rise of the upstroke (*Vmax*). Records were obtained (a) before and (b, c, d and e) 30 min after beginning the perfusion with different concentrations of Imip (10^{-7} M, 10^{-6} M, 10^{-5} M and 2.5×10^{-5} M, respectively).

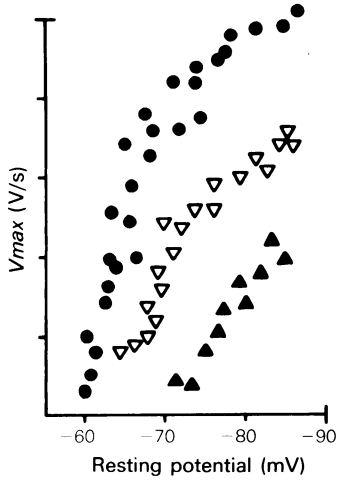

Figure 2 Effects of imipramine (Imip) on membrane responsiveness of an atrial fibre. The maximum rate of rise (V/s) is plotted on the ordinate scale and the membrane potential at the onset of depolarization (in ms) on the abscissa scale. (●) Control; Imip (▽) 5×10^{-6} M and (▲) 10^{-5} M. All perfusion periods, 30 min.

E_h, was shifted from -70.1 ± 0.8 mV to -73.2 ± 1.1. mV ($n = 6$).

The effect of Imip on the recovery of *Vmax* was studied in 12 atria. Figure 3 shows that Imip (10^{-7} M–10^{-5} M) shifted the curve downwards and to the right, slowing the recovery of *Vmax*. In the absence of the drug, *Vmax* recovered with a time constant of 24 ms and recovery time was increased to 95 ms in the presence Imip of 10^{-5} M. This prolongation of the recovery time explains the progressive increase in the ERP and the decrease observed in the *Vmax* of the first premature action potential illustrated in Figure 3.

Electrophysiological effects of chronic treatment with imipramine in atrial fibres

The effects of chronic treatment with Imip (7.5 mg/kg twice daily i.p. for 24 days) on action potential characteristics in 22 atria are shown in Table 2. The data obtained from animals treated with saline were omitted because they were not significantly different from the values obtained in non-treated animals (Table 1). As is shown in Table 2 the control values for APD_{50} and APD_{90} in Imip pretreated rat atria were not significantly different from values obtained in non-treated atria (Table 1). However, in Imip pretreated atria the resting membrane potential was significantly reduced in comparison with non-treated atria (-80.7 ± 0.4 mV as compared to -83.3 ± 0.4 mV; $P < 0.001$) and as a consequence, both the amplitude (99.5 ± 1.3 mv) and the *Vmax* (66.6 ± 1.8 V/s) of the action potential were also significantly reduced in Imip pretreated atria ($P < 0.001$).

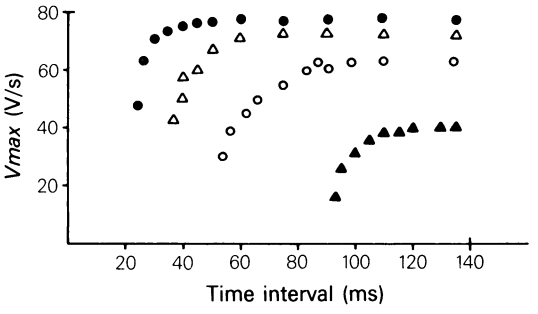

Figure 3 Effects of imipramine (Imip) on the recovery time curve in rat atrial fibres. The maximum rate of rise of premature responses expressed as percentage of the maximum rate of rise in control solution is plotted on the ordinate scale and the interval between basic driving stimuli and test stimuli on the abscissa scale. (●) Control; Imip (△) 10^{-7} M, (○) 10^{-6} M and (▲) 10^{-5} M. All perfusion periods, 30 min.

To establish whether the effects of Imip were potentiated in pretreated atria, they were superfused with different concentrations of Imip, 10^{-7} M–2.5×10^{-5} M. Results obtained after 30 min exposure to the different concentrations of Imip are shown in Table 2. Imip, as in non-treated atria, prolonged the APD_{50} and APD_{90}, reduced the amplitude and the *Vmax* of the action potential and depolarized the resting membrane potential, but changes in phase 0 characteristics were more marked in treated than in non-treated atria. Thus, in non-treated atria the resting membrane potential was reduced at concentrations $> 10^{-5}$ M and at 2.5×10^{-5} M it was depolarized to -74.6 ± 2.8 mV, whereas in Imip pretreated atria the membrane potential was depolarized at 10^{-6}M and at 2.5×10^{-5} M the depolarization level reached -64.3 ± 1.4 mV ($P < 0.001$).

Effect of imipramine on the effective refractory period

The ERP, defined as the period in which no propagated action potentials can be obtained, was evaluated in 18 experiments. The control value of ERP was 27.3 ± 1.3 ms. Table 1 shows that Imip produced a concentration-dependent lengthening of the ERP and Figure 4 shows the relation between changes in ERP and APD_{90} at different concentrations of Imip. It is evident that between 10^{-7} M and 10^{-5} M Imip the changes in ERP exceeded those in the APD, so that the points representing these variables tend to fall below the line of identity. Accord-

Table 2 Electrophysiological effects of imipramine in atrial fibres from rats treated for 24 days with imipramine (7.5 mg/kg twice daily i.p.)

Drug concentration (M)	*Resting potential* (mV)	*Amplitude* (mV)	Vmax (V/s)	*APD_{50}* (ms)	*APD_{90}* (ms)	*ERP* (ms)
0 (22)	80.7±0.4	99.5±1.3	66.5±1.8	12.1±1.2	32.0±2.1	33.1±1.9
10^{-7} (22)	80.6±0.4	98.9±1.1	64.7±1.8*	14.8±1.3**	38.2±2.6*	43.5±2.7
10^{-6} (20)	79.6±0.5***	97.3±1.3*	53.9±3.1***	16.7±1.3**	47.8±2.5***	56.6±4.2***
10^{-5} (20)	75.7±0.6***	90.1±1.2***	32.0±2.6***	22.1±3.0***	61.0±4.1***	127.5±15.8***

Values are mean ± s.e.mean. Number of observations (n) in parentheses. Readings started after 30 min of perfusion with imipramine. APD_{50} and APD_{90} refer to action potential duration measured to 50% and 90% repolarization respectively.
*$P<0.05$; **$P<0.01$; ***$P<0.001$.

ingly, the ration ERP/APD significantly increased at 10^{-7} M, 10^{-6} M and 10^{-5} M Imip from 0.86±0.04 to 0.94±0.05; 1.16±0.16 and 1.92±0.31, respectively.

In 12 Imip pretreated atria the control value of the ERP was significantly longer (33.1±1.9 ms; $P<0.001$) than in non-treated atria but Imip produced a similar concentration-dependent prolongation of the ERP (Table 2).

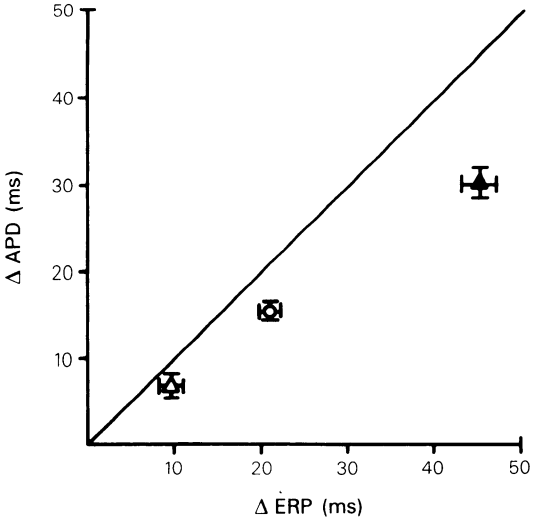

Figure 4 Effects of imipramine (Imip) on the relation between action potential duration (APD) and the effective refractory period (ERP). Mean change in APD (Δ APD) in ms is plotted on the ordinate scale and mean change in ERP (Δ ERP) in ms on the abscissa scale. Each point represents the mean of 10 experiments; bars represent the s.e.mean. Imip (△) 10^{-7} M, (○) 10^{-6} M and (▲) 10^{-5} M.

Effects of imipramine on spontaneous activity

The effects of Imip on spontaneous activity were studied in atrial fibres which were beating spontaneously at stable rates, and also in fibres in which $BaCl_2$, aconitine, ouabain or isoprenaline had enhanced the spontaneous activity.

The effects of Imip on atrial rate were studied in 10 spontaneously beating right atria. Control spontaneous rates were 194.9±15.7 beats/min. Imip decreased in a concentration-dependent manner the spontaneous activity as shown in Figure 5a. At 10^{-5} M, Imip suppressed automatic firing in 2 atria and in the other 8, atrial rate was decreased to 80.9±14.6 beats/min ($P<0.001$). Spontaneous firing ceased within 15 min of perfusion with 2.5×10^{-5} M Imip. Automaticity reappeared within 5 min of washout with control Tyrode solution. In 9 Imip pretreated atria, control automatic rates were not significantly different from those observed in non-treated atria (200.0±14.1 beats/min; $P>0.05$). At 10^{-5} M Imip suppressed the automaticity in 5 out 9 atria and in the other 4 atria the automatic rate decreased to 30.0±12.6 beats/min. Imip, 2.5×10^{-5} M caused cessation of spontaneous firing of atrial fibres 5 min after initiating perfusion. Imip also prolonged the sinus node recovery time in spontaneously beating right atria. Control values of this parameter in non-treated and Imip pretreated atria were 285.0±16.0 ms ($n=8$) and 278.0±27.0 ms ($n=8$; $P>0.05$). In non-treated atria a significant prolongation in the sinus node recovery time was observed only at 10^{-5} M Imip (Figure 5b), whereas in pretreated atria a significant prolongation was observed at concentrations $>10^{-6}$ M.

The effects of Imip on atrial fibres in which automaticity has been enhanced by $BaCl_2$, aconitine, ouabain or isoprenaline were studied in 13 right atria. In 5 atria, spontaneous activity was induced by ad-

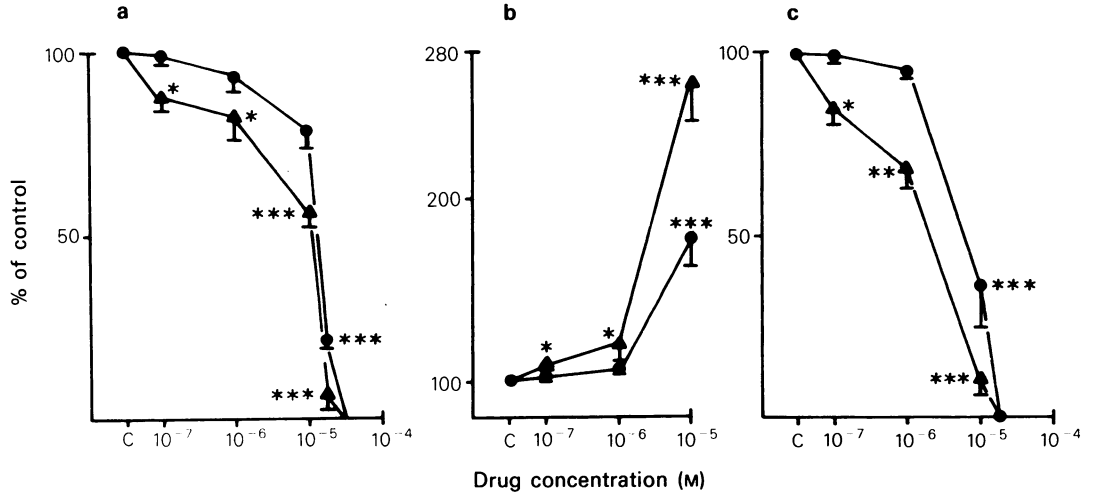

Figure 5 Effect of imipramine (Imip) on (a) atrial rate, (b) sinus node recovery time and (c) contractile force of rat isolated atria obtained from (●) non-treated and (▲) Imip pretreated rats. Atrial rate, sinus node recovery time and contractile force were plotted on the ordinate scale as percentage change and the concentration of Imip (M) on the abscissa scale. Each point represents the mean of at least 7 experiments; vertical bars represent the s.e.mean. $*P<0.05$; $**P<0.01$; $***P<0.001$.

ding 0.2 mM $BaCl_2$ to the perfusate. Figure 6a shows that Imip, 10^{-5} M, slowed the spontaneous rate. The continuous decrease in rate was associated with a decrease in the amplitude, a prolongation in the APD and a depolarization of the resting membrane potential. In these fibres the final regenerative response was followed by subthreshold oscillations which were suppressed within 2–3 min of perfusion with the membrane potential arrested at −57 mV. Once the state of low amplitude oscillations has been reached, at least 5 min was required to restore normal rate following drug washout.

The effects of Imip on the automaticity induced by ouabain (5×10^{-7} M) aconitine (10^{-6} M) and isoprenaline (10^{-6} M) were studied in another 8 right atria. As is shown in Figure 6b, Imip 10^{-5} M, slowed the spontaneous rate and effectively suppressed the automaticity as well as the low amplitude oscillations induced by ouabain. Imip, 10^{-6} M, also suppressed the increment in spontaneous rate induced by aconitine (Figure 6c) and isoprenaline (not shown). In all these experiments Imip produced effects similar to those described for Ba-induced automaticity and spontaneous rate was suppressed with the resting potential arrested at a depolarized level.

Effect of imipramine on atrial contractile force

The effect of Imip on contractile force was studied in 14 left atria driven at a basal rate of 3 Hz. Control values for the amplitude of contractions were similar in non-treated (310.6 ± 33.2 mg, $n=7$) and in Imip pretreated atria (286.2 ± 22.9 mg; $n=7$). In non-treated atria, Imip only at concentrations higher than 10^{-6} M, produced a significant decrease in contractile force (Figure 5c), whereas in pretreated atria contractile force was significantly decreased at all concentrations tested. Furthermore, in non-treated atria, contractile force was suppressed by 5×10^{-6} M whereas at 2.5×10^{-5} M Imip suppressed contractile force in Imip pretreated left atria.

In another group of experiments after 30 min of equilibration the atria were incubated in high potassium (27 mM) Tyrode solution. Adding isoprenaline (10^{-6} M) to the bath restored atrial excitability, i.e. slow responses, and the preparations were driven at a constant rate of 0.4 Hz to avoid deterioration. Imip (10^{-6} M, 10^{-5} M and 2.5×10^{-5} M) significantly reduced the amplitude of the slow contractions by $17.5\pm6.0\%$, $51.5\pm8.9\%$ and $93.4\pm3.1\%$, respectively. This negative inotropic effect was rapidly reversed following the drug washout or by increasing the external Ca concentration in the bathing media. These results seems to indicate that Ca antagonizes the depression of slow atrial contractions induced by Imip.

Discussion

The effects of Imip in a range of concentrations between 0.031 and 16.0 μg/ml were studied in rat

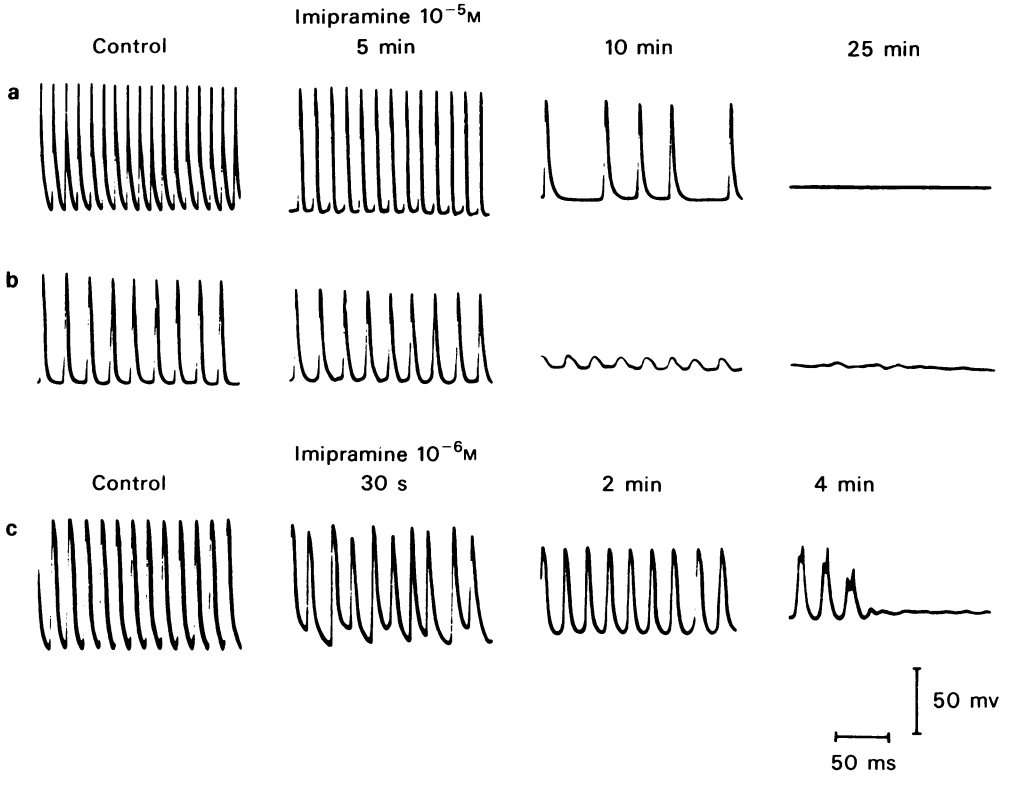

Figure 6 Effects of imipramine (Imip) on spontaneous action potentials in rat atrial fibres. Spontaneous activity was induced by adding (a) $BaCl_2$, 0.2 mM; (b) ouabain, 5×10^{-7} M or (c) aconitine, 10^{-6} M. Panels from left to right were recorded under control conditions and at different times after adding Imip 10^{-5} M to the perfusion solution. In all cases, Imip produced a pronounced decrease in the amplitude of the action potential and the spontaneous activity was suppressed with the membrane potential arrested at a depolarized level.

atrial fibres. In studies of patients treated with 30–350 mg of Imip daily, the average plasma levels ranged from 34 to 600 ng/ml (1.06×10^{-7} M to 1.87×10^{-6} M; Glassman, Perel, Shostak, Kantor & Fleiss, 1977; Biggs, 1978; Hollister, 1979); therefore, the concentrations used in this study comprised both therapeutic and toxic plasma levels attained in depressed patients treated with Imip. However, it is very difficult to equate the concentrations of Imip in the present study with the serum concentrations in man (Asberg, 1974; Glassman & Perel, 1973). Moreover, *in vivo*, Imip is rapidly desmethylated to desipramine, which has been demonstrated to be more potent than Imip in guinea-pig ventricular muscle fibres (Tamargo, Rodriguez & Garcia de Jalón, 1979).

The results of this paper demonstrate that in rat isolated atrial fibres Imip: (a) reduced action potential amplitude, *Vmax* and membrane responsiveness and this effect was enhanced in high K_o; (b) depolarized the resting membrane potential and decreased atrial excitability; (c) prolonged the APD and the ERP, increasing the ratio ERP/DPA; (d) suppressed spontaneous activity and (e) produced a negative inotropic effect. All these effects are similar to those of the so-called class I antiarrhythmics (Vaughan Williams, 1970). Therefore, the association of Imip with these drugs would be expected to increase the likelihood of cardiotoxicity. At low concentrations, $< 10^{-6}$M, Imip reduced the amplitude and *Vmax* of the action potential without altering the resting membrane potential. These results suggest that Imip inhibited the activation of the fast inward Na current in atrial fibres. Similar results have been previously described in rabbit atrial fibres (Matsuo, 1967) as well as in ventricular muscle (Auclair *et al.*, 1969; Garcia de Jalon *et al.*, 1978; Rodriguez & Tamargo, 1980) and Purkinje fibres (Rawling & Fozzard, 1979; Rodriguez & Tamargo, 1980; Weld & Bigger, 1980). At higher concentrations Imip decreased the amplitude and *Vmax* of the action potential and decreased the resting membrane potential, that exp-

lains a further reduction in phase 0 characteristics. Imip also shifted the membrane responsiveness curve to more negative values and prolonged the recovery time. Because of reduced responsiveness and a slowing of the removal of inactivation, the membrane has to repolarize to more negative values before re-excitation can occur, resulting in a prolongation of the ERP independent of any change in APD (Vaughan Williams, 1958).

In contrast to the results reported by Matsuo (1967) in rabbit atria, Imip also decreased the slope of phases 2 and 3 and prolonged the APD in rat atria. This prolongation might be caused by an increase in the slow inward Ca current (I_{si}) or by a decrease in outward current or both. Imip exerted a negative inotropic effect and reduced the amplitude of the slow contractions and this latter effect was reversed by increasing the Ca concentration in the perfusate. Thus, Imip seems to reduce the I_{si} that could explain a shortening but not the prolongation of the APD found in this paper. Therefore, it might be possible that this prolongation could be due to a decrease in K conductance. In fact, a reversible reduction in I_{si} and in outward current (IK_o, IK_i) has been reported in bovine isolated ventricular myocytes (Isenberg & Tamargo, unpublished). A decrease in I_{si} might explain the negative inotropic effect of Imip. Decreased myocardial contractility including occasional development of congestive heart failure has been reported in patients receiving therapeutic (Alexander & Nino, 1968; Jefferson, 1975) or toxic doses of Imip (Raeder, Burckhardt, Neubauer, Walter & Gastpar, 1978).

Cardiac arrhythmias may be produced by enhanced automaticity and/or depressed conduction velocity (Hoffman & Rosen, 1981). The present results demonstrate that Imip may suppress arrhythmias which may result from both mechanisms. Ouabain, aconitine, $BaCl_2$ and isoprenaline increase atrial automaticity (Hoffman & Cranefield, 1960; Trautwein, 1963) and may generate triggered activity (Cranefield, 1975). Imip decreased the sinus rate and suppressed the atrial arrhythmias induced by these four agents which suggests that it might suppress both arrhythmogenic mechanisms. This inhibitory effect cannot be attributed to an increase in K conductance since Imip suppressed the Ba-induced automaticity. A decrease in the steady-state conductance for Na and Ca ions seems a more plausible explanation. Furthermore, the decrease of phase 0 characteristics induced by Imip must be accompanied by a decrease in conduction velocity which in association with the prolongation of the ERP might block re-entry phenomena by transformation of a unidirectional into a bidirectional block. These effects could explain the ability of Imip to suppress premature atrial beats (Bigger, Giardina, Perel, Kantor & Glassman, 1977; Bigger, Kantor, Glassman & Perel, 1978). On the other hand, Imip at high concentrations depressed the sinus function and reduced the resting membrane potential and the conduction velocity that may result in the development of areas of unidirectional block and re-entry. These effects may explain the bradycardia and asystole (Jefferson, 1975; Biggs, Spiker, Petit & Ziegler, 1977) and the premature atrial complexes observed in patients with Imip plasma levels over 1000 ng/ml (Biggs *et al.*, 1977).

Chronic administration of Imip produced significant changes in the electrophysiological properties of atrial fibres. The reduction of phase 0 characteristics and the prolongation of the ERP suggest that Imip might alter the Na current kinetics, whereas the reduction of the resting membrane potential suggest that Imip might reduce K conductance. However, the dose used in this study (15 mg/kg daily) is about 10 times an average daily dosage(75–300 mg daily; Baldessarini, 1980) and plasma concentrations would be even higher than those found after an accidental overdosage. Further studies are required in chronically treated animals to define the effects of Imip.

The clinical significance of these results remains to be determined. In addition to the direct effects, Imip also exerted indirect, sympathomimetic and anticholinergic, effects (Stimmel, 1979) and the interaction between these effects have not been examined in this study. Thus, the tachycardia reported at therapeutic doses of Imip has been attributed to these indirect effects that counteract the direct negative chronotropic effect of Imip (Raisfeld, 1972). Moreover, the sympathomimetic effects shortened (Ledda, Mugelli & Mantelli, 1978), wheras the direct effects prolonged the APD, thus increasing the disparity in APD and in the recovery of atrial excitability. Both could result in atrial re-entrant rhythms *in vivo*.

References

ALEXANDER, C.S. & NINO, A. (1968). Cardiovascular complications in young patients taking psychotropic agents. *Am. Heart J.*, **78**, 757–769.

ASBERG, M. (1974). Individualization of treatment with tricyclic compounds. *Med. Clin. North Am.*, **58**, 1083–1091.

AUCLAIR, M.C., GUIDA, O. & LECHAT, P. (1969). Analyse électrophysiologique des effects de l'imipramine sur la fibre myocardique ventriculaire. *Archs int. Pharmacodyn.*, **181**, 218–231.

BALDESSARINI, R. (1980). Drugs and treatment of psychiatric disorders. In *The Pharmacological Basis of*

Therapeutics, ed. Goodman, A. Goodman, L.S. & Gilman, A. 6th ed. pp. 418–427. New York: Macmillan.

BIGGER, J. R. Jr., GIARDINA, E., PEREL, J., KANTOR, S. & GLASSMAN, A. (1977). Cardiac antiarrhythmic effect of imipramine hydrochloridrate. *N. Engl. J. Med.*, **296,** 206–208.

BIGGER, J.R. Jr., KANTOR, S., GLASSMAN, A. & PEREL, J. (1978). Cardiovascular effect of tricyclic antidepressant drugs. In *Psychopharmacology: A Generation of Progress*, ed. Lipton, M.A., DiMascio, A. & Killam, F.K. pp. 1033–1046. New York: Raven Press.

BIGGS, J. (1978). Clinical pharmacology and toxicology of antidepressants. *Hosp. Pract.*, **11,** 79–87.

BIGGS, J., SPIKER, D., PETIT, J. & ZIEGLER, V. (1977). Tricyclic antidepressant overdosage: incidence of symptoms. *J. Am. med. Ass.*, **238,** 135–138.

BRENNAN, F. (1980). Electrophysiological effects of imipramine and doxepin on normal and depressed cardiac Purkinje fibers. *Am. J. Cardiol.*, **46,** 599–606.

CRANEFIELD, P. (1975). *The Conduction of the Cardiac Impulse.* Mt. Kisko, New York: Futura Publishing Co.

GARCIA DE JALON, P., RODRIGUEZ, S. TAMARGO, J. (1978). Electrophysiological effects of imipramine in guinea-pig myocardium. *Br. J. Pharmac.*, **63,** 373P.

GLASSMAN, A. & PEREL, J. (1973). The clinical pharmacology of imipramine. *Archs. Gen. Psychiatry*, **28,** 649–653.

GLASSMAN, A., PEREL, J., SHOSTAK, M., KANTOR, S. & FLEISS, J. (1977). Clinical implications of imipramine plasma levels for depressive illness. *Archs. Gen. Psychiatry*, **34,** 197–204.

HOFFMAN, B. & CRANFIELD, P. (1960). *Electrophysiology of the Heart.* New York: McGraw Hill.

HOFFMAN, B. & ROSEN, M. (1981). Cellular mechanisms for cardiac arrhythmias. *Circulation Res.*, **49,** 1–15.

HOLLISTER, L. (1979). Monitoring tricyclic antidepressant plasma concentrations. *J. Am. Med. Ass.*, **241,** 2530–2535.

JEFFERSON, J. (1975). A review of the cardiovascular effects and toxicity of tricyclic antidepressants. *Psychosom. Med.*, **37,** 160–179.

LEDDA, F., MUGELLI, A. & MANTELLI, L. (1978). Myocardial adrenoceptors and cardiac arrhythmias. *Pharmac. Res. Commun.*, **10,** 573–588.

MATSUO, S. (1967). Comparative effects of imipramine and propranolol on the transmembrane potentials of the isolated rabbit'a atria. *Jap. J. pharmac.*, **17,** 279–286.

RAEDER, E., BURCKHARDT, D., NEUBAUER, H., WALTER, R. & GASTPAR, M. (1978). Long-term tri- and tetra-cyclic antidepressants, myocardial contractility and cardiac rhythm. *Br. med. J.*, **ii,** 666–667.

RAISFELD, I. (1972). Cardiovascular complications of antidepressant therapy: interaction at the adrenergic neuron. *Am. Heart. J.*, **83,** 129–133.

RAWLING, D. & FOZZARD, H. (1979). Effects of imipramine on cellular electrophysiological properties of cardiac Purkinje fibers. *J. Pharmac. exp. Ther.*, **209,** 371–375.

RODRIGUEZ, S. & TAMARGO, J. (1980). Electrophysiological effects of imipramine on bovine ventricular muscle and Purkinje fibres. *Br. J. Pharmac.*, **70,** 15–23.

STIMMEL, B. (1979). *Cardiovascular Effects of Mood-Altering Drugs.* pp. 134–151. New York: Raven Press.

TAMARGO, J. (1980). Electrophysiological effects of bunaphtine on isolated rat atria. *Eur. J. Pharmac.*, **62,** 81–89.

TAMARGO, J., DE MIGUEL, B. & TEJERINA, T. (1982). A comparison of josamycin with macrolides and related antibiotics on isolated rat atria. *Eur. J. Pharmac.*, **80,** 285–293.

TAMARGO, J., RODRIGUEZ, S. & GARCIA DE JALON, P. (1979). Electrophysiological effects of desipramine on guinea-pig papillary muscles. *Eur. J. Pharmac.*, **55,** 171–180.

TRAUTWEIN, W. (1963). Generation and conduction of impulses in the heart as affected by drugs. *Pharmac. Rev.*, **15,** 277–332.

VAUGHAN WILLIAMS, E. (1958). The mode of action of quinidine on isolated rabbit atria interpreted from intracellular potential records. *Br. J. Pharmac.*, **13,** 276–287.

VAUGHAN WILLIAMS, E. (1970). Classification of antiarrhythmic drugs. In *Symposium on Cardiac Arrhythmias*, ed. Sandoe, E., Flansted-Jensen, E. & Olesen, K. pp. 449–472, Söderstalje, Sweden: AB Astra.

WELD, F. & BIGGER, J.T. JR. (1980). Electrophysiological effects of imipramine on ovine cardiac Purkinje and ventricular muscle fibers. *Circulation Res.*, **46,** 167–175.

(Received September 8, 1982.
Revised November 24, 1982.)