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Effects of cetirizine on the delayed K^+ currents in cardiac cells: comparison with terfenadine

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1 The aim of the present experiments was to analyse the effect of the H_1-histamine antagonist, cetirizine, on the delayed K^+ currents in cardiac cells and to compare its effects with another H_1-histamine antagonist terfenadine, known to possess proarrhythmic effects.

2 Whole cell currents were measured by use of the single electrode patch-clamp technique in rabbit and guinea-pig myocytes.

3 The activation relationship for the I_{Kr} current in rabbit ventricular myocytes was depressed and its voltage-dependence shifted in the negative direction with a $V_{1/2}$ value -13.4 ± 2.4 mV under control conditions which changed to -19.1 ± 1.9 mV ($n=4$) in the presence of 0.1 mM cetirizine.

4 In rabbit ventricular myocytes the IC_{50} for block of I_{Kr} was 108 ± 8 μM ($n=5$); in guinea-pig ventricular myocytes this concentration of cetirizine reduced the rapidly activating component I_{Kr} to $49 \pm 4.5\%$ ($n=5$), while the slowly activating I_{Ks} was less affected and only inhibited to $79 \pm 2.3\%$ ($n=5$).

5 The block of I_{Kr} did not show use-dependence and the time course of the tail current was not changed, suggesting rested-state block or fast activated-state block and no rapid recovery on deactivation. No important difference was found in the activity of the two enantiomers of cetirizine.

6 Terfenadine in comparison was more potent in blocking I_{Kr}, the IC_{50} being 96 ± 15 nM ($n=6$).

7 Based on the present results and information in the literature on binding, it was concluded that cetirizine is a relatively selective H_1-histamine receptor antagonist, with minor effects on K^+ currents. The IC_{50} concentration for I_{Kr} block in heart cells was 1.000 times higher than the concentrations needed to block H_1 histamine receptors. The occurrence of cardiac arrhythmias due to K^+ current blockade is therefore unlikely with this drug.

Keywords: Cetirizine; terfenadine; K^+ current; single cardiac cell; arrhythmia; torsade de pointes; patch clamp

Introduction

Terfenadine, loratadine, astemizole and cetirizine are members of the second generation antihistamines and are used frequently for treatment of allergic rhinitis and urticaria (Simons, 1994). In contrast to the first generation compounds they are characterized by the absence of sedative effects due to a poor ability to cross the blood-brain barrier, probably because they are electrically charged: cetirizine at pH of 7.4 is 90.3% present as zwitterion and 9.7% as anionic base (Dogimont, UCB, personal communication). Recent reports in the literature have drawn attention to a rare though important side effect of certain members of this group at the cardiovascular level. Serious cardiac arrythmias of the torsade de pointes type have been described after high doses of terfenadine (Davies *et al*., 1989) or astemizole (Wiley *et al*., 1992; for review see Smith, 1994). This side effect has been found after overdose, or when administered in combination with drugs that interfere at the liver level with metabolic breakdown of the parent drug (such as ketoconazole and macrolide antibiotics), or under conditions that by themselves favour the occurrence of torsade de pointes such as hypokalaemia or hypomagnesaemia (Morganroth *et al*., 1993).

Torsades de pointes arrhythmia also occurs as a side effect of the use of antiarrhythmics which prolong the action potential and has been related to block of the delayed K^+ current, with consequent disturbance of the repolarization process and occurrence of early afterdepolarizations (Roden, 1993). The delayed K^+ current in heart is made up of two components, a rapidly activated, I_{Kr}, and a slowly activated I_{Ks} (Sanguinetti & Jurkiewicz, 1990). The finding that terfenadine was an efficient blocker of I_{Kr} thus provides an explanation for the occurrence of torsades de pointes in the case of overdosage (Woosley *et al*., 1993; Woosley, 1996). Although torsades de pointes arrhythmias in man have not been demonstrated to be causally related to cetirizine (Coulie *et al*., 1998), it seemed opportune to test for an eventual effect of cetirizine on the delayed K^+ currents and to compare its actions with terfenadine, an antihistamine, known to have pro-arrhythmic effects.

Methods

Cell preparation

Single cardiac ventricular cells of the rabbit and the guinea-pig were dissociated by enzymatic dispersion, following a procedure described in detail previously (Carmeliet, 1992). Rabbits and guinea-pigs were killed by intraperitoneal injection of pentobarbitone. Hearts were quickly isolated and Langendorff perfused at 37°C with (1) Ca^{2+}-free standard solution medium (see solutions) for 10 min, (2) Ca^{2+}-free standard solution containing 35 mg 50 ml^{-1} collagenase A (Boehringer-Mannheim, Mannheim, Germany) for 15 min, (3) a Ca^{2+}-free solution containing collagenase and 6.5 mg 50 ml^{-1} protease XIV (Sigma Chemical Co, St Louis, Missouri) for 35 min and (4) 0.2 mM Ca^{2+} containing solution for an extra 10 min. After isolation the cells were stored at room temperature in HEPES-Tyrode solution until used.

Electrical measurements, data acquisition and analysis

Aliquots of cells were allowed to settle on the glass bottom of a tissue bath (volume <0.5 ml) and then superfused with buffer solution (3 ml min^{-1}, 37°C). The whole-cell patch-clamp technique was used to measure individual ionic currents (Axoclamp 2-A amplifier, Axon Instruments, Foster City, California), using heat-polished borosilicate glass pipettes (horizontal puller: Zeitz Instrumente, Germany) with resistances ranging from 2 to 5 MΩ. Junction potentials were zeroed before formation of the seal. After formation of the seal, stable recordings were obtained following a 10 min dialysis. Voltage-clamp signals were low-pass filtered (5 kHz 4-pole Bessel), digitized by an A/D converter (Labmaster DMA, Scientific Solutions, Inc). Cell capacitance was measured by integrating the area of the capacitive transient elicited by a 2 or 5 mV depolarizing step from a holding potential of -50 mV and digitized at 50 kHz. Values were 196 ± 9 pF ($n=28$) for rabbit ventricular myocytes and 273 ± 14 pF ($n=14$) for guinea-pig ventricular myocytes. Series resistance was estimated by dividing the time constant of the capacitive transient by the capacitance. The time constant was 765 ± 56 μs ($n=28$) for rabbit ventricular myocytes and 1.34 ± 0.13 ms ($n=16$) for guinea-pig ventricular myocytes. The respective series resistances were 3.97 ± 0.24 MΩ ($n=28$) and 5.06 ± 0.50 MΩ ($n=16$). They were partially (40–60%) compensated without causing ringing. The voltage error for currents up to 1 nA may thus be estimated to remain smaller than 3 mV.

Pclamp software (Axon Instruments) was used to generate voltage-pulse protocols and to analyse data. In some experiments currents were directly recorded on a Gould Brush recorder 220 (-3 dB at 100 Hz, Simac, Peutie, Belgium) and analysed manually. In most experiments square depolarizing pulses of 2 s were applied from a holding potential of -50 mV; the minimum interval between pulses was 1 min. Use-dependence was measured by applying shorter depolarizing pulses of 0.2 s, repeated with an interval of 0.75 s.

To separate the two components of the delayed K^+ current, I_{Kr} and I_{Ks}, a 2 s depolarizing pulse to $+50$ mV was followed by a 2 s return to 0 mV and finally back to the holding potential of -50 mV. This protocol allows for simultaneous activation of the two components, but separate deactivation of the I_{Ks} at 0 mV and of I_{Kr} at -50 mV (Carmeliet, 1992; Heath & Terrar, 1996). The inward rectifier, I_{K1} current was measured by application of ramp voltage clamps at a speed of 50 mV s^{-1} starting from a holding potential of -50 mV and going to -110 mV.

Solutions

The extracellular solution contained in mM: NaCl 137.6, KCl 5.4, $MgCl_2$ 0.5, $CaCl_2$ 1.8, HEPES 11.6, glucose 5 and NaOH was added to pH 7.4. The pipette solution contained in mM: KCl 120, $MgCl_2$ 6, $CaCl_2$ 0.154, Na_2ATP 5, HEPES 10 with KOH until pH was 7.2. All experiments were done at 37°C.

Drugs

Cetirizine dihydrochloride and its enantiomers, ucb 28556 and ucb 28557, were a kind gift of UCB S.A. (Pharma Sector, Braine l'Alleud, Belgium). Dilutions were made from a 1 M stock solution in distilled water. Terfenadine, lot 37F0101, from Sigma (St-Louis, MO, U.S.A.) was dissolved in dimethylsulphoxide (DMSO, Sigma) to yield stock solutions of 10 mM; the vehicle at the final concentrations, did not affect the currents measured. Nisoldipine (Bayer, Wüppertal, Germany), prepared as a stock solution of 10^{-2} M in DMSO was used at a concentration of 0.2 μM to block the L-type Ca^{2+} current. Effects of drug exposure were measured after a minimum of 10 min superfusion. Washout was not systematically performed but complete reversibility could be obtained for cetirizine after 30 min of superfusion with control solution.

Statistics

Mean values ± s.e. were calculated. Significance was calculated by use of two tailed t test, unpaired or paired as specified.

Results

Activation of I_{Kr}

In rabbit ventricular myocytes the rapidly activating delayed K^+ current I_{Kr} was analysed by application of voltage clamp depolarizations from a holding potential of -50 mV to levels from -40 to $+40$ mV in increments of 10 mV. Examples of currents are shown in Figure 1. The positive holding current is due to the presence of I_{K1} at -50 mV. During the depolarizing pulse the current shifted in the inward direction, but remained net outward. For depolarizations to -40 and -30 mV the current did not show pronounced time-dependent changes. For larger depolarizations the current was composed of the transient outward current which shows a rapid activation and inactivation, and was followed by activation of I_{Kr}. On return to the holding potential a tail current was observed which was larger the greater the depolarization during the preceding pulse. In the conditions used in the present experiments the tail currents were entirely due to deactivation of the I_{Kr} (Carmeliet, 1993). In the presence of cetirizine 0.1 mM, holding current and the initial transient outward current during the pulse were not changed. The currents during the remaining part of the depolarizations and especially the tail currents were less outward. Figure 2 summarizes the results obtained in four similar experiments. The results were normalized by taking the tail amplitude under control conditions for a depolarization to 20 mV as 100%. This value corresponded to $0.81 \pm$

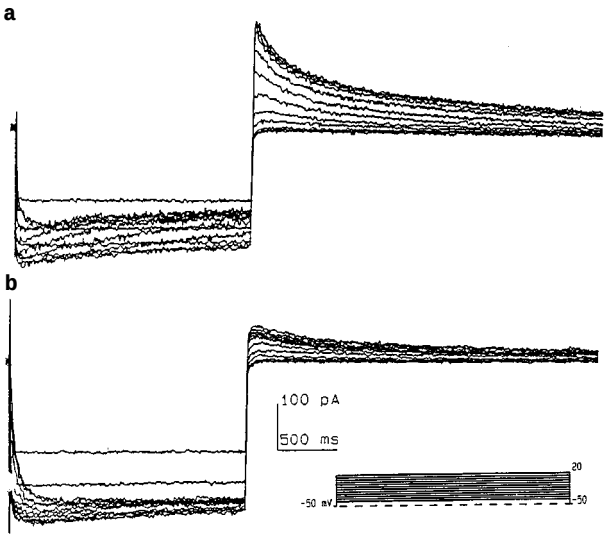

Figure 1 Effect of cetirizine on membrane currents obtained for 2 s voltage clamps from a holding potential of -50 mV to depolarized levels up to 20 mV in increments of 10 mV. (a) Control records; (b) in the presence of cetirizine 0.1 mM. Rabbit ventricular myocyte. Temperature 37°C.

0.07 pA pF^{-1} ($n=4$). In the absence of the drug the current was activated from -30 mV onwards and saturated at about 0 mV; midvoltage was -13.4 ± 2.4 mV and the slope was 5.9 ± 0.3 mV. In the presence of the drug the activation curve was depressed (saturating value: 0.29 ± 0.03 pA pF^{-1}), with a midvoltage of -19.1 ± 1.9 mV and a slope of 6.6 ± 0.4 mV ($n=4$). Midvoltage difference was statistically significant ($P=0.01$; paired, two tailed t test); slope factors were not significantly different.

Concentration-effect relationships

The effect of different concentrations of cetirizine on the I_{Kr} was studied by measuring the reduction in tail current amplitude. Cells were subjected to voltage clamp depolarizations of 2 s to 20 mV from a holding potential of -50 mV. Cetirizine was added in increasing concentrations from 10 μM to 1 mM. Each concentration was studied during 10 min, at which time a steady-state effect was obtained. Similar experiments were performed with terfenadine in concentrations ranging from 30 nM to 1 μM. The results are summarized in Figure 3. Control currents were 0.50 ± 0.05 pA pF^{-1} and 0.63 ± 0.05 pA pF^{-1}, respectively for terfenadine and cetirizine experiments. For cetirizine the IC_{50} was 108 ± 8 μM and the Hill coefficient 1.37 ± 0.23 ($n=5$). For terfenadine the corresponding values were 96 ± 15 nM and 1.58 ± 0.13 ($n=6$).

Block by cetirizine was not use-dependent

Use-dependent block is a block which enhances with an increase in frequency of stimulation (use or activation of the channel). Drugs that show use-dependence are potentially better antiarrhythmics, since they inhibit the current and prolong the refractory period preferentially at high frequencies, while their arrhythmogenic potentiality at low frequencies remains low.

The existence of use-dependence was measured by applying short (0.2 s) depolarizing pulses repetitively (interval of 0.75 s), following a rest for 5 min at the holding potential. Figure 4 shows examples of currents during the depolarizing pulse (lower level) and the successive tails (upper level). Under control conditions the tail currents showed a small summation because of incomplete deactivation during the 'diastolic' period at the holding potential. In the presence of cetirizine 100 μM, the current during the pulse as well as the tail was reduced. Upon repetition the tail amplitude barely changed. In the case of use-dependent block, the tails should decrease as the pulse is repeated (see Figure 7 in Carmeliet (1993)). Four experiments of this type were performed. The tail current at the end of the first pulse was 1.02 ± 0.10 pA pF^{-1} under control conditions and was reduced to 0.61 ± 0.06 pA pF^{-1} in the presence of the drug. At the end of the series (30 pulses) the tail increased by $14\pm2\%$ under control conditions and by $12\pm3\%$

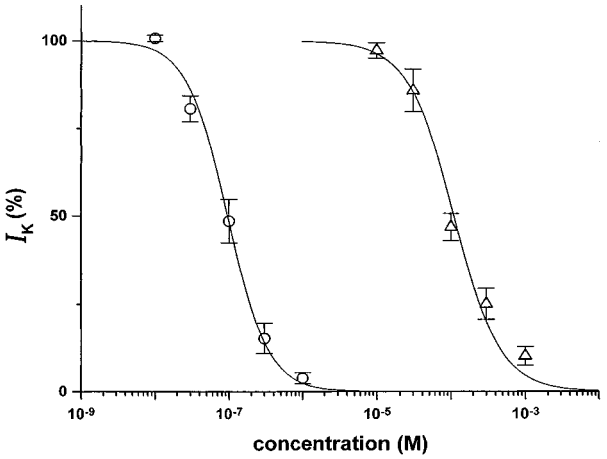

Figure 3 Concentration-effect curves for terfenadine (circles; $n=6$) and cetirizine (triangles; $n=5$). Ordinate scale: I_{Kr} as %; abscissa scale: molar concentration of drug. Effects were quantified by fitting the results using the following equation: $(1+([D]/IC_{50})^{n_H})^{-1}$, where [D] is the drug concentration, IC_{50} is the drug concentration for 50% efficiency, and n_H is the Hill coefficient. Rabbit ventricular myocytes.

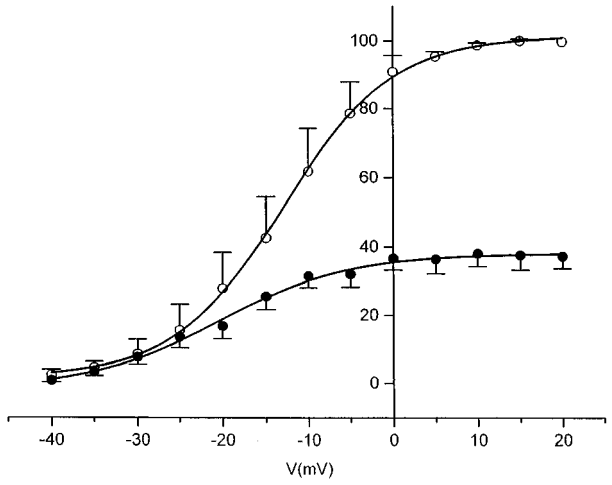

Figure 2 Activation curve of I_{Kr} current under control conditions (open circles) and in the presence of cetirizine 0.1 mM (solid circles). Data are normalized tail currents (means with vertical lines showing s.e.; $n=4$) obtained at -50 mV following a 2 s clamp to different depolarized levels. Tail amplitude for a depolarizing pulse to 20 mV under control conditions was taken as 100%. Full lines are Boltzmann relations from the equation: $I/I_{max}=[1+\exp(V_{1/2}-V_t)/s)]^{-1}$, where I_{max} corresponds to the maximum plateau value of the tail currents, V_t the test potential, $V_{1/2}$ the half-maximum activation potential and s the slope factor. Rabbit ventricular myocytes.

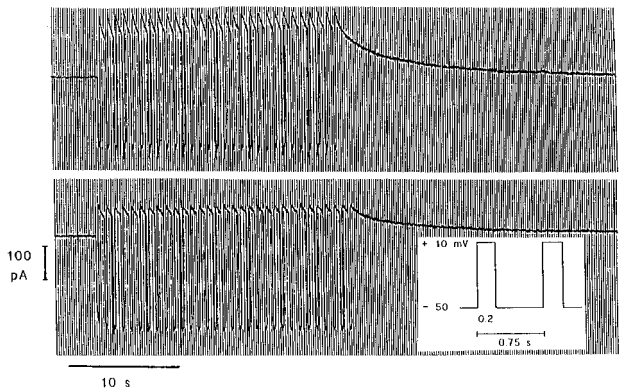

Figure 4 Absence of use-dependent block. Following a 1 min rest at the holding potential of -50 mV, the cell was subjected to a series of voltage clamp depolarizations of 0.2 s duration to 10 mV. Interval between depolarizing clamps was 0.75 s (see inset). Downward deflections are currents during the depolarization, upward deflections are tail currents. During control (top) the amplitude of the tail current showed a small summation due to incomplete deactivation during the interval at the holding potential. In the presence of cetirizine 0.1 mM (bottom) the first tail current already was reduced to about half the control value and this decrease did not show any summation. Rabbit ventricular myocyte. Similar results were obtained in three other cells.

in the presence of the drug. Block of the current therefore was not changed during repetitive stimulation.

Effect of the two enantiomers of cetirizine on I_{Kr}

For the wild type human H_1 receptor expressed in CHO cells the pK_i of the ucb 28566 and ucb 28557 were respectively 8.5 and 7.0 (Moguilevsky *et al.*, 1995). The effect of the two enantiomers at a concentration of 0.1 mM on I_{Kr} was measured by applying voltage clamps of 2 s duration to 20 mV from a holding potential of −50 mV and measuring the change in tail amplitude. The two substances were studied in separate experiments. Control values for the tail currents were 0.55 ± 0.04 pA pF^{-1} ($n=5$) and 0.49 ± 0.04 pA pF^{-1} ($n=5$) in the two series. ucb 28556 was slightly more effective than ucb 28557. Mean relative current in the presence of the drug was $45\pm1.7\%$ ($n=5$) for ucb 28556 and $65\pm24\%$ ($n=5$) for ucb 28557, the effect was statistically significant at the 0.001 level (unpaired, two tailed *t* test).

Does cetirizine block I_{Ks}

Depending on activation and deactivation kinetics, blocking characteristics and modulation by hormones and transmitters, two components of the delayed K^+ current can be distinguished (Sanguinetti & Jurkiewicz, 1990). The effect of cetirizine and terfenadine was studied on the two components applying a voltage clamp protocol which allowed the direct differentiation of the two components (see Methods). The clamp consisted of a depolarizing pulse of 2 s to +50 mV, followed by a clamp to 0 mV during which most of I_{Ks} deactivated, but I_{Kr} remained fully activated, and finally a return to the holding potential of −50 mV, where I_{Kr} deactivated. In control conditions the amplitudes of I_{Kr} and I_{Ks} were respectivley, 0.97 ± 0.07 pA pF^{-1} and 1.17 ± 0.06 pA pF^{-1} ($n=12$).

Examples of the currents are given in Figure 5a,b. At 0.1 mM cetirizine the tail at 0 mV was only slightly diminished but was reduced to about 50% at −50 mV. The reduction of outward current during the pulse to 50 mV and the shift in the inward direction at 0 mV should thus be interpreted as entirely due to block of I_{Kr}. Experiments were also done with 1 mM cetirizine and quantitative data are summarized in Table 1. At 0.1 mM cetirizine in 5 preparations, I_{Kr} was reduced to 49% whereas I_{Ks} only to 79%. At 1 mM cetirizine I_{Kr} decreased to 16% and I_{Ks} to 56% in 9 cells.

Similar differential effects on the two I_K components were obtained for terfenadine (Figure 5b for an example and Table 1 for mean results with three concentrations 0.1, 0.3 and 1.0 μM). In general the effects were similar to those for cetirizine, with greater block of I_{Kr} than I_{Ks}. At high concentrations (Figure 5b) terfenadine also shifted the holding current in the inward direction, an effect which can be explained by a fall in I_{K1} conductance.

The I_{K1} *current*

The I_{K1} or inward rectifier is the K^+ current responsible for the resting potential and the final repolarization phase of the action potential. The effect of cetirizine on the I_{K1} was investigated by applying voltage-clamp ramps at a speed of 50 mV s^{-1} over a broad range of potentials, as shown in Figure 6. At 0.1 mM no effect was seen at potentials positive to the resting potential, but a small reduction became manifest at hyperpolarized potentials. Four experiments were performed with a concentration of 1.0 mM. An estimation of the effect was made either by measuring the change in current at −60 mV or by measuring the relative decrease in inward current at −90 mV, taking as reference the current at the cross-over potential of the two current-voltage relations which is also a measure of the reversal potential. Control currents were 4.3 ± 0.2 pA pF^{-1} at −60 mV and 11.4 ± 2.1 pA pF^{-1} at

Table 1 Block of the two I_K components in guinea-pig ventricular myocytes

Drug	*Concentration*	I_{Ks}	I_{Kr}	n
Cetirizine	0.1 mM	79.0 ± 2.3	49.0 ± 4.2	5
	1.0 mM	56.4 ± 1.8	16.0 ± 2.2	9
Terfenadine	0.1 μM	95.3 ± 2.5	44.3 ± 5.0	3
	0.3 μM	77.7 ± 1.4	24.7 ± 7.0	3
	1.0 μM	45.6 ± 4.8	5.9 ± 2.0	3

Data shown are means±s.e. % of current remaining.

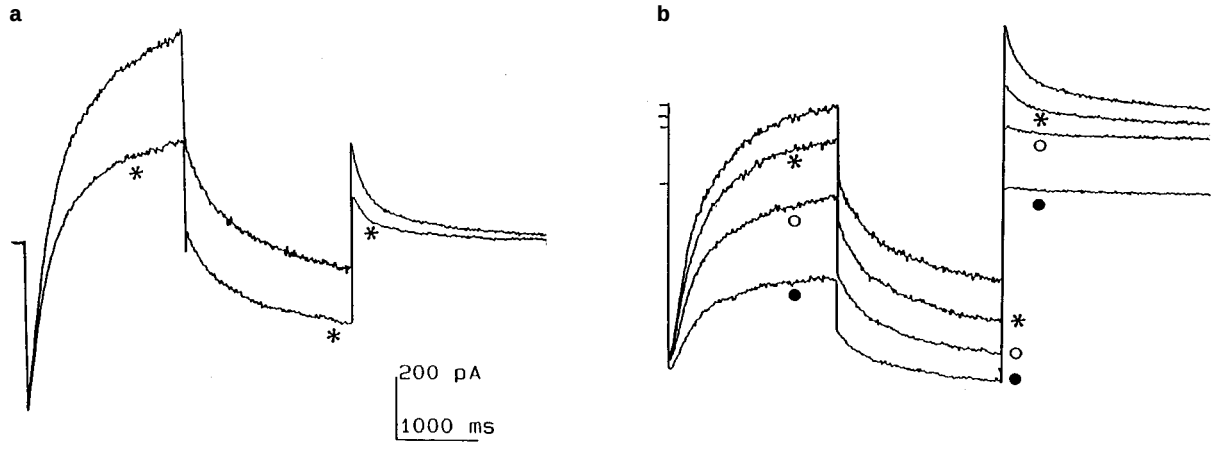

Figure 5 Differential block of I_{Kr} and I_{Ks} in guinea-pig ventricular myocytes by cetirizine (a) and terfenadine (b). The voltage protocol consisted of a 2 s depolarization to 50 mV followed by a return for 2 s to 0 mV and finally back to the holding potential of −50 mV. This protocol allows for simultaneous activation of the two components during depolarization at 50 mV but separate deactivation of I_{Ks} at 0 mV and of I_{Kr} at −50 mV. From the amplitude of the tail currents and their change at 0 and −50 mV the effect of drug on the two components can be evaluated. The concentration of cetirizine was 0.1 mM; the concentration of terfenadine was changed from 0.1 μM (star), to 0.3 μM (open circle) and to 1.0 μM (solid circle). The two substances blocked preferentially I_{Kr}. Terfenadine also blocked I_{K1} in a concentration-dependent way (shift of the holding current in the inward direction).

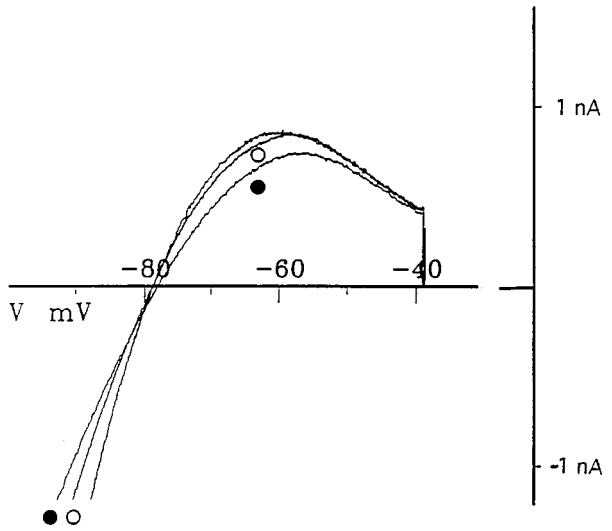

Figure 6 Effect of cetirizine on the inward rectifier, I_{K1}. Ramp voltage clamps were applied at a speed of 50 mV s^{-1} starting from a holding potential of −40 mV and going to −110 mV. Guinea-pig ventricular myocyte. Concentrations of cetirizine were 0.1 (open circle) and 1.0 mM (solid circle). Only the higher concentration caused a small shift in the inward direction.

−90 mV. In the presence of 1 mM cetirizine the current decreased to 79.8±4.0% at −60 mV and at −90 mV to 60±5.6% ($n=4$).

Discussion

The experiments on rabbit ventricular myocytes showed that cetirizine reduces the amplitude of the tail currents at −50 mV. In a previous paper (Carmeliet, 1992) it was demonstrated that under the experimental conditions used the tails at −50 mV in rabbit ventricular myocytes were blocked by dofetilide, known to affect selectively I_{Kr} (Jurkiewicz & Sanguinetti, 1993). It may thus be concluded that cetirizine also blocks the rapid I_{Kr} delayed K^+ current. The block did not increase with repetition of the depolarizing pulse, in other words the block did not show any use-dependence. This means either that block is already present at rest for the closed channel and does not change with activation (real tonic block), or occurs so rapidly upon activation that it is complete during the first depolarizing pulse of 0.2 s duration of a series (fast activation block). The fact that the activation curve for I_{Kr} was slightly shifted in the negative direction is consistent with the existence of activated-state block (difference in affinity between the closed and activated state; law of microscopic reversibility). The time course of the tail currents was not changed, indicating that recovery from block was absent or occurred very slowly upon deactivation. From these observations it may be extrapolated that block of I_{Kr} by cetirizine will not vary with frequency.

The experiments on guinea-pig ventricular myocytes have shown that cetirizine blocks both the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed K^+ current in cardiac tissue, but inhibition was more pronounced for I_{Kr}. Both currents are present in the human cardiac tissues (Beuckelmann *et al*., 1993; Konarzewska *et al*., 1995; Veldkamp *et al*., 1995), but their relative density is not known. The effect on the two currents was studied by using a voltage clamp protocol that allowed for simultaneous activation of the currents but separate deactivation of I_{Ks} at 0 mV and I_{Kr} at −50 mV. The validity of this procedure has been demonstrated by block of the tail currents at −50 mV and only minor effect on the tails at 0 mV or −10 mV, in the case of dofetilide (see Figure 10 in paper by Carmeliet (1992)) and in the case of E4031 (see Figure 6 in paper by Heath & Terrar (1996)).

Cardiotoxic side effects of antihistamines, which take the form of torsade de pointes arrhythmia, have been shown to be related to block of delayed K^+ currents (Roden, 1993; Woosley & Sale, 1993). In order to evaluate the risk of arrythymias as a possible side effect it is thus necessary to compare the relative concentrations required for antihistamine activity and for K^+ current block. The binding affinity of cetirizine and terfenadine for guinea-pig cerebellar and lung H_1 receptors has been shown to be similar with pK_i values of 6.8 to 7.5 (Leysen *et al*., 1991; Ter Laak *et al*., 1993). For human H_1 receptors expressed in Chinese hamster ovary cells pK_i values were 8.5 and 8.2 for terfenadine and cetirizine, respectively (Moguilevsky *et al*., 1995). The potency of cetirizine to block I_{Kr} (K_d of 0.1 mM) is thus 1000 to 10.000 times less than its affinity to block H_1 receptors. Because of this large difference the complication of torsade de pointes as a consequence of I_{Kr} block is less probable than in the case with terfenadine, where binding to the H_1-receptor and block of I_{Kr} (IC_{50} of 96 nM) occur at similar concentrations.

Terfenadine in general is less specific than cetirizine: the IC_{50} for terfenadine for binding to Ca^{2+} channels (measured by inhibition of verapamil and nitrendipine binding) occurs at 0.2 and 0.44 μM, while no effect is seen at concentrations above 10 μM for cetirizine (Snyder & Snowman, 1987). Terfenadine also blocks other K^+ currents, such as I_{to} and I_{Kur} in human atrial cells (Crumb *et al*., 1995), and the Kv.1.5 channel expressed in L-cells (Yang *et al*., 1995) or in HEK cells (Crumb *et al*., 1995). The Kv.1.5 current has similar activation kinetics and pharmacological properties as the I_{Kur}. The interaction with terfenadine is characterized by open channel block (Rampe *et al*., 1993; Yang *et al*., 1995).

A further difference between cetirizine and terfenadine is the absence of any important metabolism of cetirizine. Interference with metabolism of the parent drug at the level of the liver by certain antibiotics (Hanrahan *et al*., 1995) or antifungal substances (Morganroth *et al*., 1993; Smith, 1994) is thus of less importance for cetirizine since most of the drug is eliminated in its native form.

Our estimation of the IC_{50} of 96 nM for I_{Kr} block for terfenadine in the rabbit heart was close to the value of 180 nM estimated for the cat heart (Woosley *et al*., 1993). In guinea-pig ventricular myocytes I_K was shown to be rather insensitive to terfenadine, with only 9.5% decrease at the very high concentration of 10 μM (Berul & Morad, 1995); in this study no distinction was made between the two current components. In the present experiments the effect of cetirizine and terfenadine was smaller for I_{Ks} than for I_{Kr}, a result which may to some extent but incompletely explain the insensitivity of the complex current in the guinea-pig.

Although the block of I_{Kr} by the two enantiomers of cetirizine was statistically different, the difference was small and is of no practical importance. The two enantiomers of terfenadine also have similar electrophysiological effects: they prolong QT and the effective refractory period to the same extent in the guinea-pig heart (Pinney *et al*., 1995) and block the cloned Kv1.5 channel expressed in L-cells (Yang *et al*., 1995).

In a recent letter to The Lancet, Lindquist and Edwards (1997) compared cardiac risks for a number of non-sedating antihistamines on the basis of spontaneous adverse drug reaction reports of the WHO. Complications in patients taking

cetirizine included cardiac rhythm disorders and two cases of death. However, this study is incomplete in that there was no control data, i.e. it does not take into account the spontaneous rates of background cardiac events in a population not taking the drug. Up to now no case of torsade de pointes has been causally related to the intake of cetirizine (Coulie *et al*., 1998).

It is concluded that cetirizine in comparison with terfenadine is a less potent blocker of K^+ currents, whereas its antihistamine activity is similar. Thus complications due to arrythmogenic effects based on block of K^+ currents are less probable with cetirizine.

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References

BERUL, C.I. & MORAD, M. (1995). Regulation of potassium channels by nonsedating antihistamines. *Circulation,* **91,** 2220 – 2225.

BEUCKELMANN, D.J., NABAUER, M. & ERDMANN, E. (1993). Alterations of K^+ currents in isolated human ventricular myocytes from patients with terminal heart failure. *Circ. Res.,* **73,** 379 – 385.

CARMELIET, E. (1992). Voltage- and time-dependent block of the delayed K^+ current in cardiac myocytes by dofetilide. *J. Pharmacol. Exp. Ther.,* **262,** 809 – 817.

CARMELIET, E. (1993). Use-dependent block and use-dependent unblock of the delayed rectifier K^+ current by almokalant in rabbit ventricular myocytes. *Circ. Res.,* **73,** 857 – 868.

COULIE, P., DELAERE, A., DE VOS, Ch., DONELLY, F. & RIHOUX, J.P. (1998). Non-sedating antihistamines and cardiac arrhythmias. *The Lancet,* **351,** 451.

CRUMB, W.J., WIBLE, B., ARNOLD, D.J., PAYNE, J.P. & BROWN, A.M. (1995). Blockade of multiple human cardiac potassium currents by the antihistamine terfenadine: possible mechanism for terfenadine-associated toxicity. *Mol. Pharmacol.,* **47,** 181 – 190.

DAVIES, A.J., HARINDRA, V., MCEWAN, A. & GHOSE, R.R. (1989). Cardiotoxic effect with convulsions in terfenadine overdose. *Br. Med. J.,* **298,** 325.

HANRAHAN, J.P., CHOO, P.W., CARLSON, W., GREINEDER, D., FAICH, G.A. & PLATT, R. (1995). Terfenadine-associated ventricular arrhythmias and QTc interval prolongation. A retrospective cohort comparison with other antihistamines among members of a health maintenance organization. *Ann. Epidemiol.,* **5,** 201 – 209.

HEATH, B.M. & TERRAR, D.A. (1996). Separation of the components of the delayed rectifier potassium current using selective blockers of iKr and IKs in guinea-pig isolated ventricular myocytes. *Exp. Physiol.,* **81,** 587 – 603.

JURKIEWICZ, N.K. & SANGUINETTI, M.C. (1993). Rate-dependent prolongation of cardiac action potentials by a methanesulfonanilide class III antiarrhythmic agent. Specific block of rapidly activating delayed rectifier K^+ current by dofetilide. *Circ. Res.,* **72,** 75 – 83.

KONARZEWSKA, H., PEETERS, G.A. & SANGUINETTI, M.C. (1995). Repolarizing K^+ currents in nonfailing human hearts, subepicardial ventricular myocytes. *Circulation,* **92,** 1179 – 1187.

LEYSEN, J.E., GOMMEREN, W., JANSSEN, P.F., SANZ, G., GILLARDIN, J.M., SCHOTTE, A. & JANSSEN, P.A. (1991). Antihistaminiques non-sédatifs et liaison aux récepteurs histaminiques-H1 centraux et périphériques. *Allerg. Immunol. Paris,* **23,** 51 – 57.

LINDQUIST, M. & EDWARDS, I.R. (1997). Risks of non-sedating antihistamines. *The Lancet,* **349,** 1322.

MOGUILEVSKY, N., VARSALONA, F., GUILLAUME, J.-P., NOYER, M., GILLARD, M.J., DALIERS, J.-P.H. & BOLLEN, A. (1995). Pharmacological and functional characterization of the wild-type and site-directed mutants of the human H1 histamine receptor stably expressed in CHO cells. *J. Receptor Signal Transduction Res.,* **15,** 91 – 102.

MORGANROTH, J., BROWN, A.M., CRITZ, S., CRUMB, W.J., KUNZE, D.L., LACERDA, A.E. & LOPEZ, H. (1993). Variability of the QTc interval: impact on defining drug effect and low-frequency cardiac event. *Am. J. Cardiol.,* **72,** 26b – 31b.

PINNEY, S.P., KOLLER, B.S., FRANZ, M.R. & WOOSLEY, R.L. (1995). Terfenadine increases the QT interval in isolated guinea pig heart. *J. Cardiovasc. Pharmacol.,* **25,** 30 – 34.

RAMPE, D., WIBLE, B., BROWN, A.M. & DAGE, R.C. (1993). Effects of terfenadine and its metabolites on a delayed rectifier K^+ channel cloned from human heart. *Mol. Pharmacol.,* **44,** 1240 – 1245.

RODEN, D.M. (1993). Torsade de pointes. *Clin-Cardiol.,* **16,** 683 – 686.

SANGUINETTI, M.C. & JURKIEWICZ, N.K. (1990). Two components of cardiac delayed recitifer K^+ current. Differential sensitivity to block by class III antiarrhythmic agents. *J. Gen. Physiol.,* **96,** 195 – 215.

SIMONS, F.E.R. (1994). H_1-Receptor antagonists. Comparative tolerability and safety. *Drug Safety,* **10,** 350 – 380.

SMITH, S.J. (1994). Cardiovascular toxicity of antihistamines. *Otolaryngol. Head Neck Surg.,* **111,** 348 – 354.

SNYDER, S.H. & SNOWMAN, A.M. (1987). Receptor effects of cetirizine. *Ann. Allergy,* **59,** 4 – 8.

TER LAAK, A.M., DONNE OP DEN KELDER, G.M., BAST, A. & TIMMERMAN, H. (1993). Is there a difference in the affinity of histamine H1 receptor antagonists for CNS and peripheral receptors? An in vitro study. *Eur. J. Pharmacol.,* **232,** 199 – 205.

VELDKAMP, M.W., VAN GINNEKEN, A.C., OPTHOF, T. & BOUMAN, L.N. (1995). Delayed rectifier channels in human ventricular myocytes. *Circulation,* **92,** 3497 – 3504.

WILEY, J.F.D., GELBER, M.L., HENRETIG, F.M., WILEY, C.C., SANDHU, S. & LOISELLE, J. (1992). Cardiotoxic effects of astemizole overdose in children. *J. Pediatr.,* **120,** 799 – 802.

WOOSLEY, R.L. (1996). Cardiac actions of antihistamines. *Annu. Rev. Pharmacol. Toxicol.,* **36,** 233 – 252.

WOOSLEY, R.L., CHEN, Y., FREIMAN, J.P. & GILLIS, R.A. (1993). Mechanism of the cardiotoxic actions of terfenadine. *J. Am. Med. Assoc.,* **269,** 1532 – 1536.

WOOSLEY, R.L. & SALE, M. (1993). QT interval: a measure of drug action. *Am. J. Cardiol.,* **72,** 36b – 43b.

YANG, T., PRAKASH, C., RODEN, D.M. & SNYDERS, D.J. (1995). Mechanism of block of a human cardiac potassium channel by terfenadine racemate and enantiomers. *Br. J. Pharmacol.,* **115,** 267 – 274.

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