

Effect of H₁ antihistamines upon the cardiovascular system

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The antihistamines are among the most widely prescribed drugs in the world. For the treatment of allergic diseases. The first generation antihistamines, such as hydroxyzine, dexchlorpheniramine or diphenhydramine, among others, pose the inconvenience of inducing sedative effects and – depending on the molecule involved – anticholinergic, alpha-adrenergic or other actions that limit their usefulness. The introduction of the new second generation, non-sedating antihistamines represented an important advance in the treatment of different allergic disorders, and particularly rhinoconjunctivitis.

These new drugs, which are ever increasing in number (astemizole, terfenadine and fexofenadine, cetirizine and levocetirizine, loratadine and desloratadine, ebastine, mizolastine and rupatadine, as the most salient examples), are relatively free of side effects and offer a broad therapeutic spectrum. However, in the last decade of the twentieth century, reports began to appear of *torsades de pointes* (TdP) type arrhythmias, arrhythmias, syncope and even sudden death, fundamentally related with astemizole [1] and terfenadine [2], which generated considerable concern and drew attention to the cardiac effects of the antihistamines.

Histamine exerts a series of actions upon the cardiovascular system. Thus, through mediation of the H₁ and H₂ receptors, histamine increases vascular permeability and induces hypotension, with reflex tachycardia. In turn, at heart muscle level, histamine action upon the H₁ receptors induces an increase in atrioventricular node conduction, while the H₂ receptors mediate positive chronotropic and inotropic effects [3]. The H₁ antihistamines, as inverse agonists, exert the opposite effect, with partial countering of the aforementioned actions. However, the main concern in relation to the cardiovascular safety of the antihistamines refers to their cardiac arrhythmogenic potential. A review is provided below of the principles and clinical particulars of these worrisome adverse effects.

Cardiac action potential

In order to correctly understand the effect of antihistamines upon the heart, a brief reminder of the cardiac action potential is indicated. The surface electrocardiogram (ECG) records the electrophysiological process whereby electric impulses are generated and conducted through the heart muscle tissue. Thus, the P wave represents the electrophysiological action potential of the atria, while the QRS complex reflects the ventricular action potential (which masks atrial repolarization), and the T wave corresponds to ventricular repolarization. In turn, the QT interval, which extends from the Q wave to the end of the T wave, reflects the duration of the action potential plus the time associated with electric impulse transmission through the ventricles. The QT interval, which usually has a duration of between 200-300 ms, must be less than 440 ms in males and 460 ms in females. Above these limits we speak of a prolongation of the QT interval (or long QT), and the risk of ventricular arrhythmias increases. Nevertheless, it should be stated that a correction must be applied to the QT value, to avoid alterations attributable to heart rate.

The cardiac action potential is generated by the combined action of different ion channels that induce different ion input and output currents (Figure 1). In the same way as other cells, the interior of the cardiac cells is negatively charged with respect to the exterior, with a resting transmembrane potential difference of –80 to –90 mV, which is close to the electrochemical potential for potassium ions, due to the high K⁺ conductance under resting conditions. However, cardiac cells are excitable, and an adequate stimulus serves to sequentially open and close a series of membrane ion channels, giving rise to changes in the transmembrane potential difference that in turn produce the cardiac action potential (Figure 1). Basically, and starting from the negative baseline

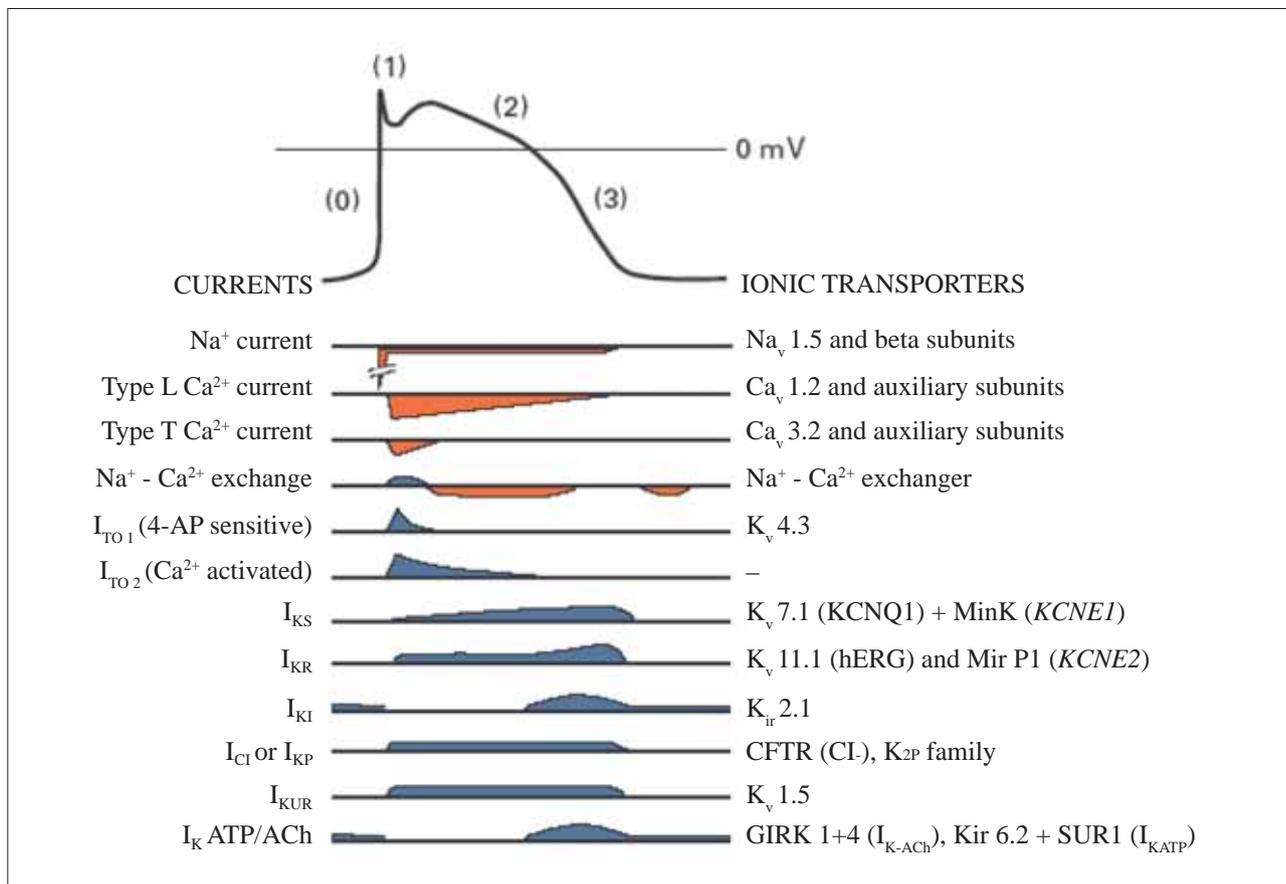


Figure 1. Cardiac action potential and ionic currents. Reproduced with permission from [9]. See text for explanation.

resting value (due to the high potassium conductance), a fast depolarizing Na^{2+} influx current (referred to as I_{Na}) is produced, giving rise to phase 0 of the cardiac action potential; the action of this current modifies the potential difference from -90 mV to $+30$ mV [4,5]. This in turn is followed by a transient potassium efflux current (I_{to}), responsible for a small repolarization taking place immediately afterwards, and which represents phase 1 of the cardiac action potential. This current is very important in rats and mice, due to their high heart rates, though not so in other species such as the dog, guinea pig, weasel or humans. During the plateau phase (phase 2), the action potential is maintained by the effect of a Ca^{2+} ion influx current (ICa). The repolarization phase (phase 3) is due to the efflux of K^{+} ions, fundamentally as a consequence of the effect of the so-called fast (I_{Kr}) and slow components (I_{Ks}), the late rectifying potassium current, which induce repolarization and gradually return the action potential to its resting state. The last phase (phase 4), referred to as the diastolic depolarization phase, is due to the decrease in activity of the two late rectifying current components, and to the effect of the input pacemaker current (I_{f}), and the weak background sodium influx current ($I_{\text{Na-B}}$). There are also other, different potassium channels in the heart [6],

which when blocked can give rise to different effects upon the cardiac action potential.

The no less than 8 potassium currents described for the heart [7] show different opening and closing characteristics, as well as differences in time dependence, frequency and voltage, and in terms of their regulation and the effects of drugs. Each of these currents exerts a different effect upon the action potential, though under normal conditions the main currents that participate in repolarization of the action potential are the late rectifying potassium current (I_{Kr} and I_{Ks}), the influx rectifying current (I_{Ki}), and the transient efflux current (I_{to}). Drug-induced arrhythmias are fundamentally mediated by drugs that suppress the I_{Ki} and I_{kr} channels, which control the fast repolarization phase. Although it was initially speculated that the first of these two channels was responsible for TdP induced by antihistamines [8], it was subsequently shown that the main cardiac adverse effects of the antihistamines are attributable to IKr current block.

Determination of the QT interval [9]

For determination of the QT interval it is preferable

Table 1. Normal values of the QT interval, corrected according to the Bazett formula (modified from Yap and Camm) [84]. The values are expressed in milliseconds.

	Normal	Limiting	Prolonged
Adult males	<430	430-450	>450
Adult females	<450	450-470	>470
Children	<440	440-460	>460

to record the surface ECG at a speed of 50 mm/s and with an amplitude of 0.5 mV/s, using a multichannel system capable of simultaneously recording all 12 leads. To measure the QT interval, we trace a line tangential to the zone of greatest slope of the descending portion of the T wave. The intersection point between this tangent and the isoelectric line defines the end of the T wave. The interval between the start of the QRS complex and the end of the T line in turn defines the length of the QT interval. The small physiological U waves should not be included in measurement of the QT interval. It is preferable to determine the interval from the second axial lead (DII), because on this lead the repolarization vectors tend to give rise to a single wave instead of a T wave and a U wave. Nevertheless, the U waves that are not separated from the T wave are considered to be pathological, and can be included in the QT interval.

The QT interval is influenced by heart rate. Therefore, 3-4 RR intervals before the QT interval are to be measured to correct for frequency. Posteriorly, we apply one of several possible correction formulas. The most widely used formulas are those of Bazett ($QT_c = QT/RR^{1/2}$) and Fridericia ($QT_c = QT/RR^{1/3}$). The former is more popular, though the latter is more exact for extreme heart rate values. RR is expressed in seconds, as a result of which in both cases, when $RR = 1$, i.e., the heart rate is 60 beats per minute (bpm), the $QT_c = QT$. The normal values are reported in Table 1.

At present, new repolarization parameters are being considered, such as QT dispersion (maximum – minimum QT interval), for assessing the efficacy and safety of drugs [10]. An update of the methods used to evaluate drug-induced TdP has been published by Hoffman and Warner [11].

On the other hand, the QT interval also varies according to patient gender, being longer in women – probably because their cardiac cells generate lesser repolarization currents [12]. Recently, the concept of cardiac repolarization reserve has been introduced, defined as a physiological reserve found in each individual to counter exogenous or endogenous factors capable of affecting cardiac repolarization. This reserve is extremely variable and may be reduced in some individuals. In the case of women, the concept could explain their tendency to develop TdP when taking medicines that control the QT interval [13]. In some cases a genetic basis may exist, such as in the frustrated form of long QT syndrome [14].

Long QT syndrome

The long QT syndrome (LQTS) is one of the best known heart diseases. Since its first description, important advances have been made in our knowledge of its electrophysiological and genetic bases. In 1957, Jervell and Lange-Nielsen described the electrocardiographical principles of the disorder, in a description of four deaf children – three of which died prematurely – and who presented a prolongation of the QT interval [15]. From the historical perspective, as early as 1856 Meissner [16] described the case of a deaf girl who suffered a collapse and died after being punished in school. The girl had two siblings that also died after an episode of fright and anger, respectively. Following the description by Jervell and Lange-Nielsen, other congenital cases without deafness began to be reported [17,18], yielding a total of ten familial long QT syndromes (see Table 2). Developments in genetics have made a fundamental contribution to the subject, by allowing linking analyses, which have shown that of the genes associated with familial long QT syndrome, the majority encode for subunits of the ion channels found in the heart (Table 2).

The first such gene to be linked to familial long QT syndrome was the HERG gene (human ether-a-go-go related gene), thus named after being cloned by homology with another potassium channel called ether-a-go-go [19], responsible for LQT2 (one of the types of familial long QT syndrome, of recessive autosomal inheritance). This gene encodes for the alpha subunit of the voltage-dependent potassium channel that mediates the fast component of the late rectifying potassium current, I_{KR} . It has been suggested that HERG1 mutations alter this current and induce a delay in repolarization –

Table 2. Congenital and acquired forms of long QT syndrome. Reproduced from Abriel et al [9].

Long QT syndrome: congenital forms

Romano-Ward syndrome: LQT1-LQT6

Jervell and Lange-Nielsen syndrome: J-LN1 and J-LN2

Associated to Andersen syndrome: AND1 or LQT-7

Associated to syndactyly

Long QT syndrome: acquired forms

Antiarrhythmic drugs (class IA, IC and III)

Other drugs (antibiotics, antifungals, psychotropic agents, etc.)

Heart disease (heart failure, myocardopathy, etc.)

Electrolytic disorders: hypopotassemia, hypocalcemia, hypomagnesemia

Nutritional disorders (alcoholism, anorexia, etc.)

Others

LQT: long QT syndrome; J-LN: Jervell and Lange-Nielsen syndrome; AND: Andersen syndrome

which in turn represents a mechanism for triggering TdP [20]. Nevertheless, there are different types of familial long QT syndrome that affect different ion channels, with diverse hereditary patterns, and some are more over associated with other anomalies.

In addition to the congenital etiology of long QT syndrome, there are a series of acquired causes [21]. Among them, mention may be made of certain cardiac diseases such as congestive heart failure or myocardopathies; hydroelectrolytic disturbances such as hypocalcemia, hypopotassemia or hypomagnesemia; the use of antiarrhythmic drugs such as those corresponding to classes IA, IC and III; the use of other drugs such as antibiotics, antifungals or psychotropic agents; or certain nutritional disorders (Table 2).

From the above it can be inferred that there are a series of risk factors implicated in the possibility of developing long QT syndrome and TdP, including the following [21]: Female gender (71% of all patients), heart disease (41%), the administration of two or more QT-prolonging drugs (39%), or hypopotassemia (28%). In only 18% of cases is there a family history of long QT syndrome (LQTS), a previous TdP episode, or a clearly prolonged QT interval before drug ingestion. Other potential risk factors are liver failure or the consumption of certain foods – fundamentally grapefruit juice, which contains furanocoumarins, which in turn are potent inhibitors of the CYP3A4 isoenzyme and induce rapid loss of intestinal enzyme activity – though they do not inhibit liver CYP3A4 [22].

The HERG gene

Molecular biological studies have shown I_{KR} to be the result of the heteromeric binding of subunits encoded for by the HERG and MiRP genes (KCNE2) [23]. The HERG (human ether-a-gogo related gene) encodes for the alpha subunit of the voltage-dependent potassium channel that mediates the fast component of the late rectifying potassium current, $Kv11.1$ (I_{KR}). The HERG gene was originally cloned in 1994 from a systematic search of a human hippocampus gene library [24]. The purported structure of the HERG channel, comprising 1159 amino acids, shows it to be similar to other members of the voltage-dependent potassium channel family. Basically (Figure 2), these channels consist of four subunits, each containing 6 alpha-helix transmembrane domains and a loop conforming the “pore region” [25]. The transmembrane domains (S1-S6) are functionally organized so that domains S5 and S6, and the loop of the pore region, constitute the channel pore, while domain S4 includes a series of charged and regularly spaced amino acids that function as a voltage sensor [26]. Both the carboxyterminal and the aminoterminal extreme are located within the cells. The I_{KR} channel encoded for by the HERG gene is one of the main channels implicated in human ventricular repolarization.

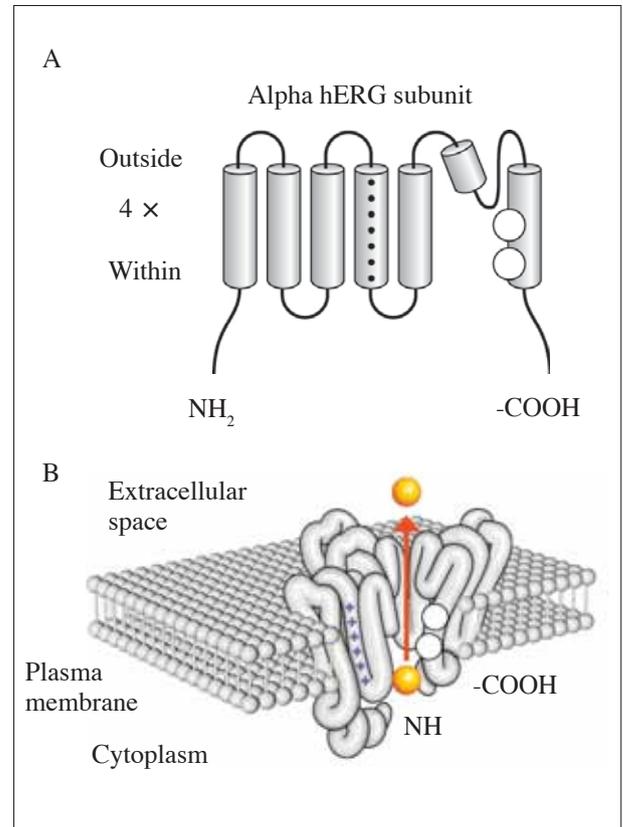


Figure 2. Structure of the HERG potassium channel. Reproduced with permission from [9]. See text for explanation.

Most drugs capable of prolonging the QT interval do so by blocking the HERG channel ($Kv11.1$). However, the opposite does not always apply. In effect, in the clinical setting, the hypothyroidism, the administration of amiodarone and the presence of severe hypocalcemia induce a marked prolongation of the QT interval, though this is only rarely associated with TdP – unless concomitant water-electrolyte alterations are present [27]. A characteristic common to the three processes is the fact that they induce marked inhibition of the type L Ca^{2+} currents (I_{CaL}). Moreover, treatment with magnesium also attenuates the flow of Ca^{2+} towards the interior of the cell, and is effective in abolishing the arrhythmia in TdP – though it fails to completely normalize the QT interval [28].

Citalopram, a specific serotonin reuptake inhibitor (SSRI), blocks the HERG channel at concentrations similar to those of other tricyclic antidepressants, though it also blocks I_{CaL} [29]; this protective effect of I_{CaL} block may explain the low fatal toxicity associated with the SSRIs [30]. As regards the reason why the drugs specifically block this channel, mention should be made of two recently described principal characteristics of the channel. On one hand, and unlike the other channels, it lacks two proline groups in segment S6; in other

channels, these amino acids induce an acute angle – thus markedly reducing the pore volume. However, Kv11.1 lacks this angle, and consequently its pore volume is much greater – thus making it possible to accommodate chemical structures much larger than in the case of the other potassium channels [31]. On the other hand, the channel possesses two aromatic amino acids (tyrosine and phenylalanine) that allow interaction with aromatic rings present in drugs that are able to block receptors of this kind [9]. There have even been descriptions of polymorphisms in the encoding gene that may condition increased susceptibility to this effect.

Methods for studying the effects of drugs upon the Kv11.1 channel

A number of methods have been developed for evaluating the effects of drugs upon the Kv11.1 potassium channel. On one hand, evaluations can be made in mammalian cell lines or in oocytes of *Xenopus laevis* genetically manipulated to specifically express this channel [32]. On the other hand, there are also experimental electrophysiological models, including human myocytes, though full-heart systems have also been developed, as well as Purkinje fiber models, or papillary muscle and ventricular muscle preparations of different species (e.g., dogs, rabbits or guinea pigs). These models offer the advantage of being able to detect QT interval prolongation regardless of the ion current affected [33]. Among the non-electrophysiological techniques, mention may be made of fluorescence systems that use voltage-sensitive dyes, and radioactively-labeled dofetilide (a known I_{Kr} channel blocker) competitive inhibition tests.

Evaluations also may be made *in vivo* by evaluating the electrocardiographic changes induced by drugs in anesthetized or conscious animals. To this effect dogs are used, as well as monkeys, rabbits, pigs and guinea pigs. Studies in conscious animals without movement limitations are preferred. Although such studies are not very predictive as refers to the arrhythmogenic potential of a drug, in view of the differences between the different species and humans in terms of cardiac electrophysiology, they do offer the advantage of simulating pathological conditions such as hypopotassemia, bradycardia, etc., more closely similar to the clinical setting, and allow the use of pharmacological models of arrhythmia.

A detailed analysis of the evaluation methods is beyond the scope of the present review, however. Updated recommendations on the procedures for evaluating the arrhythmogenic potential of non-antiarrhythmic drugs are available (www.ich.org/LOB/media/MEDIA_2192.pdf).

The new antihistamines and the induction of arrhythmias

During the nineties, some drugs without effects upon

the cardiovascular system, including the antihistamines terfenadine and astemizole, were seen to be able to trigger *torsades de pointes*-type arrhythmias, susceptible to inducing tachycardia or ventricular fibrillation, or even death [34]. In most cases these phenomena were associated to absolute [35-38] or relative overdose, due to pharmacological interactions with compounds that inhibit the P450 cytochrome system [39-44], thereby increasing the concentration of the drug. Interactions with antiarrhythmic drugs were rarely responsible [45]. In other instances the disorders occurred in the context of some background heart disease or water-electrolyte disturbance [46]. Other studies have demonstrated interactions between terfenadine and grapefruit juice, resulting in reduced metabolism of the drug and a significant prolongation of the QT interval [47-49].

Although it has been estimated that the incidence of *torsades de pointes* (TdP) associated with the use of terfenadine or astemizole is very low, since antihistamines are fundamentally prescribed for the treatment of disorders that pose no threat to patient life, such as rhinoconjunctivitis or urticaria, any life-threatening adverse effect requires very careful evaluation. As has been commented above, the reports of ventricular arrhythmias induced by terfenadine and astemizole led to research on the potential influence of the new antihistamines upon the Kv11.1 channels. A summary is provided below of the effects upon these channels of the second generation antihistamines that are currently available on the Spanish market. In turn, Table 3 reports the recommendations in this sense, reflected in the Spanish Vademecum on the internet (www.vademecum.medicom.es). Nevertheless, prior mention is required of the fact that the induction of arrhythmias of this kind is not an inherent and general effect of the second generation antihistamines [50-53], and is only associated with some compounds of this drug class, such as astemizole or terfenadine.

1) Astemizole and its active metabolites

Both astemizole and demethylastemizole block the Kv11.1 channels [54-57]. It seems that norastemizole inhibits these channels at higher doses, as a result of which it may have a better safety profile from the cardiological perspective [55].

2) Terfenadine and fexofenadine

Terfenadine is known to be able to block the Kv11.1 potassium channels [56,58-62]. As has already been commented, and in the same way as with astemizole, the arrhythmogenic effects occur in the context of absolute or relative drug overdose.

On the other hand, fexofenadine does not seem to affect the HERG potassium channel [53,63,64,]; doses of up to 1400 mg during one week have been administered to healthy volunteers, without QT prolongation [65]. In this same study, no prolongation of the interval appeared to occur as a result of interaction with ketoconazole or erythromycin.

Table 3. Recommendations regarding possible cardiac effects, found in the Spanish Vademecum on the internet (www.vademecum.medicom.es), in reference to the main second generation antihistamines used in Spain.

Drug substance	Interactions with other drugs and other forms of interaction	Contraindications	Special warnings and special precautions for use
Rupatadine	<p>The concomitant administration of rupatadine and ketoconazole or erythromycin respectively induces a 10- and 2- to 3-fold increase in systemic exposure to rupatadine. Therefore, it is not advisable to use rupatadine with these drugs and in general with other CYP3A4 isoenzyme inhibitors.</p> <p>These modifications were not accompanied by changes in QT interval, and were not associated with an increase in adverse effects versus the drugs administered separately.</p>	Hypersensitivity to rupatadine.	Rupatadine 10 mg tablets should not be combined with ketoconazole, erythromycin or any other potential inhibitor of isoenzyme CYP3A4 of the P450 cytochrome system, since these drug substances increase the plasma concentration of rupatadine.
Mizolastine	<p>Although the bioavailability of mizolastine is high and the drug is mainly metabolized via glucuronidation, the systemic dosing of ketoconazole and erythromycin moderately increases the plasma concentration of mizolastine, and concomitant use is therefore contraindicated. The concomitant use of other potent inhibitors or substrates of liver oxidation (cytochrome P450 3A4) with mizolastine must be carried out with caution. Such drugs include cimetidine, cyclosporine and nifedipine.</p>	<p>Hypersensitivity to mizolastine.</p> <p>Concomitant dosing with systemic imidazole antifungals or macrolide antibiotics.</p> <p>Important impairment of liver function.</p> <p>Clinically relevant heart disease or a history of symptomatic arrhythmias.</p> <p>Patients with suspected or known QT prolongation or electrolyte imbalances, particularly hypopotassemia.</p> <p>Clinically significant bradycardia.</p> <p>Drugs known to prolong the QT intervals, such as class I and III antiarrhythmic agents.</p>	<p>Mizolastine has a weak capacity to prolong the QT interval in some subjects.</p> <p>The degree of prolongation is moderate and has not been associated with cardiac arrhythmias.</p> <p>Elderly patients may be particularly susceptible to the sedative effects of mizolastine and to the potential effect of the drug upon cardiac repolarization.</p>
Loratadine	<p>Due to the broad therapeutic margin of loratadine, no clinically relevant interactions are expected, and none have been documented in the clinical trials conducted to date.</p>	Loratadine is contraindicated in patients with hypersensitivity to the drug substance or to any of the excipients in the drug formulation.	*
Desloratadine	<p>No clinically relevant interactions have been reported in clinical trials with desloratadine tablets administered together with erythromycin or ketoconazole.</p>	Hypersensitivity to the drug substance or to any of the excipients, or to loratadine.	*
Cetirizine	<p>To date, no interactions with other drug substances are known. Studies with cetirizine have revealed no clinically relevant interactions (with pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam). In a multiple dose study with theophylline (400 mg once a day), a slight decrease was observed (16%) in cetirizine clearance, while the availability of theophylline was not altered by the concomitant administration of cetirizine.</p>	Hypersensitivity to cetirizine, to any component of the drug formulation, or to any piperazine derivative.	*

Drug substance	Interactions with other drugs and other forms of interaction	Contraindications	Special warnings and special precautions for use
Levocetirizine	No interaction studies have been made with levocetirizine (including studies with CYP 3A4 inducers). Studies involving racemic cetirizine have revealed no clinically relevant interactions (with pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam). In a multiple dose study with theophylline (400 mg once a day), a slight decrease was observed (16%) in cetirizine clearance, while the availability of theophylline was not altered by the concomitant administration of cetirizine.	Hypersensitivity to levocetirizine, to any component of the drug formulation, or to any piperazine derivative. Patients with terminal kidney disease and creatinine clearance < 10 ml/min.	*
Ebastine	Studies have been made of the interaction of ebastine in combination with ketoconazole or erythromycin (both compounds prolong the QTc interval). Both combinations have revealed pharmacokinetic and pharmacodynamic interactions, giving rise to increased plasma ebastine levels – though the increase in QTc interval was only about 10 ms greater than with ketoconazole or erythromycin alone. It is therefore advisable to administer ebastine with caution to patients concomitantly receiving ketoconazole and erythromycin.	Hypersensitivity to ebastine or to any of the excipients.	Caution is required when administering to patients with known cardiac risk, such as those with QT prolongation, hypopotassemia, or concomitant treatment with drugs that prolong the QT interval or inhibit isoenzyme CYP3A4, such as theazole antifungals or macrolide antibiotics.

*No mention of cardiac adverse events

3) Cetirizine and levocetirizine

Hydroxyzine, a compound from which cetirizine is derived, does not appear to induce ventricular arrhythmias, though T wave changes have been reported, associated with high doses of this drug [34]. Its metabolite, cetirizine, is fundamentally eliminated through the kidneys, with scant liver metabolization. Cetirizine does not block the Kv11.1 channels, even at high concentrations, and in different models and circumstances [7,50,53,57,62,66-68], and the drug has only rarely been associated with cardiac adverse effects. It is presumed that levocetirizine, an enantiomer of cetirizine, exhibits a similar cardiological profile [50,64].

4) Ebastine and carebastine

Ebastine is able to interact with the potassium channels, though in general no cardiac adverse effects have been reported. In a study in which up to 5 times the therapeutic dosage was administered, no significant modification of the QT interval was observed [69-71]. Nevertheless, caution is advised in patients with a long QT interval who are using drugs that affect the P450 cytochrome system, or who present hypopotassemia [69,70]. Carebastine does not appear to block the potassium channels [34].

5) Loratadine / desloratadine

Some studies have demonstrated a certain effect on the

part of loratadine upon the Kv11.1 potassium channels. Thus, Crumb [72], in transfected human embryonic kidney cells, reported a blocking effect on the HERG channel similar to that induced by terfenadine. However, Taglaitela et al [67], in a model of *Xenopus laevis* oocytes with heterologous HERG channel expression, found loratadine to induce much less inhibition than terfenadine and astemizole – though cetirizine produced no inhibitory effect in this model. However, these concentrations are unlikely to be reached under usual clinical conditions [46]. The concomitant dosing of loratadine with drugs that inhibit CYP3A4 increases the concentrations of the former, though generally without QT modification – except when the concomitantly administered drug is nefazodone [73]. Overall, it seems that loratadine exerts no clinical effect upon the potassium channels [50,53,64,74]. In turn, desloratadine does not appear to block the potassium channels [50,75-77].

6) Mizolastine

Mizolastine is structurally similar to astemizole, though it is much more lipophilic. Mizolastine binds to the Kv11.1 potassium channel at a concentration much higher than the usual therapeutic concentrations reached, and may induce a degree of channel block [78]. In healthy volunteers, mizolastine caused no changes in QT interval at normal doses [79-81], or at doses up to

Table 4. Practical approach to the prescription of non-antiarrhythmic drugs capable of prolonging the QT interval.

Risk	Definition	Prior ECG	Follow-up ECG	Cardiological consultation	ECG monitorization
Very low	Without risk factors	Unnecessary	Unnecessary	Unnecessary	Unnecessary
Low	Women without risk factors	Unnecessary	Unnecessary	Unnecessary	Unnecessary
Medium	Heart disease	Advisable	Advisable	Advisable	Advisable
High	Drug interactions	Necessary	Necessary	Necessary	Questionable
Very high	History of LQTS	Obligate	Obligate	Obligate	Obligate

LQTS: long QT syndrome. Reproduced from Abriel et al (9).

four times greater than the doses administered in clinical practice [79].

7) Rupatadine

Rupatadine concentration increases when the drug is administered with molecules that inhibit the P450 cytochrome system, though it does not appear to prolong the QT interval, even when administered with erythromycin or ketoconazole [82]. On the other hand, rupatadine binds to the Kv1.5 potassium channel at a concentration much higher than the levels afforded by the usual therapeutic doses; no significant clinical effect is thus to be expected [83].

Prevention

As has been commented above, a series of risk factors are associated to the induction of arrhythmias by certain drug substances. Therefore, a good measure of caution is the identification of those patients that have certain risk factors – generally based on the compilation of an adequate clinical history – before administering any drug in general, and an antihistamine in particular. Three possible questions which the physician should raise before administering an antihistamine have been proposed [33]:

1. Does the patient have any form of heart disorder? If so, then an antihistamine with little or no effect on the Kv1.1 potassium channels should be selected.

2. Is the patient receiving any of the following drugs: macrolides, opiates, imidazoles, antipsychotic agents, antimalarials or antimigraine medication? If so, then prescription should be carried out with caution, since these agents can also prolong cardiac repolarization.

3. Does the patient present any of the described risk

factors, such as special diets (grapefruit juice), liver disease, electrolyte disorders, etc.? If so, then the specific recommendations applicable to each case should be followed.

For non-antiarrhythmic drugs with a potential to prolong the QT interval, it also has been suggested that patients should be classified by risk group, with intervention accordingly. The recording of an ECG before and after administration of the drug, or consultation with a cardiologist have even been proposed (Table 4) [9]. Nevertheless, these recommendations are not based on clinical studies.

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