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Blockade of Cardiac Potassium and Other Channels by Antihistamines

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Abstract

The use of terfenadine and astemizole, two long-acting nonsedating histamine H_1 receptor antagonists, has been associated with prolongation of the QT interval, development of ventricular arrhythmias, particularly torsade de pointes, and sudden cardiac death. Both drugs block the rapidly activating component of the delayed rectifier channel, I_{Kr}. At much higher concentrations, they also block several other cardiac channels (Na^+, Ca^{2+}, K^+). Since many other antihistamines can also block one or other of the cardiac ion currents (e.g. loratadine blocks the human cardiac K^+ channel, hKv1.5, with the same potency as terfenadine), these results are also reviewed and their clinical relevance discussed.

Because of the proarrhythmic risk, some antihistamines should be taken only at the recommended doses and avoided in patients with liver disease or in those taking medications that inhibit oxidative cytochrome P-450 enzymes. These drugs should also be avoided in those with the congenital long QT syndrome or with secondary forms of delayed repolarisation (hypokalaemia, bradycardia, drug-induced QT prolongation). Identification of predisposing factors could enable physicians to anticipate, and thereby avoid, this potentially lethal complication of antihistamine therapy.

Histamine H_1 receptor antagonists are a group of structurally diverse compounds frequently prescribed for the relief of symptoms of upper respiratory tract infections, allergy or urticarial conditions. Because the use of older antihistamines was limited by their anticholinergic and sedative properties, new long-acting and nonsedating antihistamines were developed. These drugs had fewer adverse effects, and it was assumed that they were safer than the older agents; thus, some are available without prescription.

Unfortunately, the use of terfenadine and astemizole has been associated in some patients with an excessive prolongation of the electrocardiographic QT interval, resulting in torsade de pointes, a life-threatening polymorphic ventricular tachycardia, and sudden cardiac death.[1] Torsade de pointes appears to be a common adverse effect of all drugs that delay repolarisation and produce an excessive prolongation of cardiac action potential duration (APD). Moreover, it has very recently been reported that other nonsedating antihistamines (loratadine, acrivastine, cetirizine) can induce cardiac arrhythmias and sudden death.[2]

The clinical circumstances in which the proarrhythmic effects of antihistamines have occurred include drug overdosage and severe hepatic dysfunction, or concomitant administration of other drugs that inhibit the metabolism of antihistamines (table I). Most antihistamines undergo rapid and extensive biotransformation in the liver via the oxidative cytochrome P-450 (CYP) enzymatic

Table I. Risk factors for torsade de pointes in patients taking antihistamines

Conditions that increase serum levels of antihistamines
Drug overdosage
Hepatic dysfunction (alcoholic cirrhosis, hepatitis)
Drug-induced inhibition of hepatic metabolism: macrolides (erythromycin, clarithromycin, troleandomycin), oral antifungals (itraconazole, ketoconazole, miconazole), cimetidine
Grapefruit juice flavonoids
Concomitant administration of antihistamines with drugs, or conditions, leading to QT prolongation
Drugs
antiarrhythmic drugs: quinidine, disopyramide, *d*-sotalol, dofetilide, ibutilide
psychotropics: phenothiazines, tricyclic antidepressants
antibacterials: macrolides, pentamidine, cotrimoxazole (trimethoprim/sulfamethoxazole)
others: diuretics, oral antifungals, ketanserin, cisapride, probucol, anthracyclines, organophosphate compounds, prenylamine, bepridil
Conditions
myocardial ischaemia, acidosis, congestive heart failure, hypothyroidism, bradyarrhythmias, electrolyte disorders (hypokalaemia, hypomagnesaemia)
female gender
congenital long QT syndrome

system. Thus, even in apparently healthy patients, coadministration of potentially cardiotoxic antihistamines with drugs that inhibit their hepatic metabolism can result in dangerously high plasma concentrations of the antihistamine, abnormal QT prolongation and torsade de pointes. Other circumstances in which proarrhythmic effects of antihistamines have occurred are coadministration with drugs or conditions leading to delayed repolarisation and QT prolongation, and the presence of the congenital long QT syndrome.[1]

1. Prolongation of Action Potential Duration and Refractoriness

Figure 1 shows that cardiac repolarisation reflects a delicate balance between inward and outward currents during the plateau phase. Thus, prolongation of the APD and the QT interval by antihistamines may result from the blockade of outward K^+ currents that delay repolarisation and/or the activation of depolarising inward Na^+ (I_{Na}) and L-type Ca^{2+} currents (I_{Ca}) that prolong the plateau of the action potential. Present evidence indicates that antihistamines prolong cardiac APD and refractoriness by blocking one or more cardiac K^+ channels.[1,3-7]

Cardiac voltage-gated K^+ channels represent the most diverse group of ion channels. They control APD, modulate pacemaker activity, maintain the resting potential and are molecular targets for drugs that prolong the APD. Under physiological conditions, the main K^+ currents participating in cardiac repolarisation include the following: (i) the transient outward K^+ current (I_{Kto}) responsible for the early rapid repolarisation; (ii) the delayed rectifier K^+ currents, which represent a composite of ultrarapid (I_{Kur}), rapid (I_{Kr}) and slow (I_{Ks}) components; and (iii) the inward rectifier current (I_{K1})

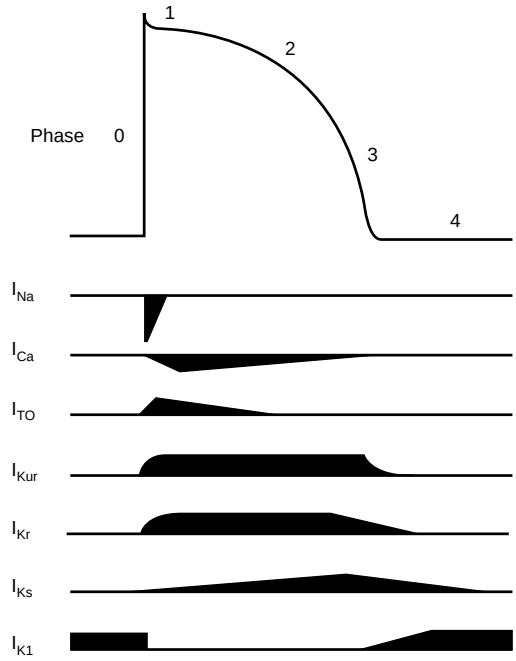

Fig. 1. Schematic representation of the individual ion currents involved in generating the ventricular cardiac action potential. I_{Na} = inward Na^+ current; I_{Ca} = inward L-type Ca^{2+} current; I_{Kto} = transient outward K^+ current; I_{Kur}, I_{Kr} and I_{Ks} = ultrarapid, rapid and slow delayed rectifier K^+ currents, respectively; I_{K1} = inward rectifier K^+ current.

Table II. Effects of antihistamines on cardiac ion channels. Data are expressed as IC_{50} values (concentrations producing 50% inhibition of the current) or as the percentage of blockade at 10 μmol/L (except where indicated)[a]

Drug	I_{Kto}	I_{Kr}	*HERG*	I_{Ks}	hKv1.5	I_{K1}
Terfenadine	11%[b,4]	50 nmol/L[3]	0.2-0.3 μmol/L[11,12]	58%[3]	1.1 μmol/L[7]	20-39%[3,4]
Astemizole	23%[4]	1.5 nmol/L[3]	48 nmol/L[12]	0.3%[3]		5-25%[3,4]
Loratadine	12%[5]	5%[b,5]	5%[b,5]	58%[5]	1.2 μmol/L[6]	
Ebastine	~2%[b,11]	~65%[b,11]	41%[b,11]	~30%[b,11]	6.5%[b,7]	<5%[b,11]
Chlorpheniramine		1.1 μmol/L[3]	21 μmol/L[12]	9.7%[3]		0.6%[3]
Pyrilamine		1.1 μmol/L[3]		16.3%[3]		1.3%[3]
Diphenhydramine			27 μmol/L[12]			
Cetirizine		108 μmol/L[13]		44%[c,13]		20%[c,13]

a I_{Kr}, I_{Ks} and I_{K1} were recorded in isolated guinea-pig and rabbit ventricular myocytes and I_{Kto} was recorded in rat cardiomyocytes. The cloned *HERG* channel was expressed in *Xenopus* oocytes.

b Percentage of blockade at 1 μmol/L.

c Percentage of blockade at 1 mmol/L.

HERG = human erg-related gene; **hKv1.5** = human cardiac K^+ channel; $\mathbf{I_{Kr}}$ and $\mathbf{I_{Ks}}$ = rapid and slow delayed rectifier K^+ currents, respectively; $\mathbf{I_{K1}}$ = inward rectifier K^+ current; $\mathbf{I_{Kto}}$ = transient outward K^+ current.

responsible for the final rapid repolarisation and the maintenance of the resting potential.

2. Polymorphic Ventricular Tachycardia

Two hypotheses have been proposed to explain drug-induced torsade de pointes.[8] One suggested that excessive prolongation of the APD (promoted during bradyarrhythmias, hypokalaemia or therapy with APD-prolonging drugs) can lead to surges of transient depolarising inward currents (mainly I_{Ca}) during repolarisation, which are manifested as early after-depolarisations (EADs) and triggered arrhythmias (torsade de pointes). Both terfenadine and astemizole have induced APD prolongation and EADs in multicellular cardiac preparations. The second hypothesis suggested that regional dispersion of repolarisation predisposes to re-entrant rhythms as a result of heterogeneity in refractoriness among regions in the circuit. In fact, there is a correlation between QT dispersion and the development of torsade de pointes.

The immediate management of torsade de pointes includes elimination of precipitating factors (table I), shortening of the APD [by cardiac pacing, isoprenaline (isoproterenol) infusion] or administration of drugs that block the I_{Ca} [intravenous magnesium, calcium antagonists (verapamil, diltiazem)].[9]

3. Blockade of Cardiac Voltage-Gated Ion Channels by Antihistamines

3.1 Blockade of I_{Kr}

The rapidly activating cardiac delayed rectifier, I_{Kr}, is characterised by rapid activation at –50mV and marked inward rectification due to fast inactivation at positive test potentials.[10] The major α subunit of the human cardiac I_{Kr} is encoded by a human erg-related gene (*HERG*). Heterologous expression of *HERG* in *Xenopus* oocytes produced a K^+ current nearly identical to I_{Kr} in cardiomyocytes, and mutations of the *HERG* gene have been identified as the cause of the chromosome 7-linked form of the congenital long QT syndrome (LQT2).[10] Thus, *HERG* dysfunction/inhibition can produce congenital or drug-induced long QT syndrome.

Table II shows that nonsedating antihistamines block I_{Kr} at concentrations significantly lower than those required to block other ion currents. I_{Kr} antagonists markedly prolong the QT interval and may cause torsade de pointes; thus, the blockade of this current may underlie the proarrhythmic effects of antihistamines. Surprisingly, chlorpheniramine and mepyramine block I_{Kr} rather weakly, which explains why these agents did not prolong the QT interval at therapeutic plasma concentra-

tions.[3] The IC_{50} values (concentrations producing 50% inhibition of I_{kr}) were higher in *HERG* channels expressed in *Xenopus* oocytes than in native channels, probably because of drug accumulation in the oocyte yolk sac.

Unlike most other K^+ currents, the magnitude of I_{Kr} is reduced on lowering of extracellular potassium ($[K]_o$). This explains why hypokalaemia results in disproportionate QT prolongation and induction of torsade de pointes in patients receiving I_{Kr} antagonists.[14,15] Additionally, most I_{Kr} blockers exhibit 'reverse' use dependency, resulting in a more marked QT prolongation at slower heart rates. This renders antihistamines proarrhythmic, especially after long diastolic intervals (bradyarrhythmias, compensatory pauses after an ectopic beat).[3,16]

Most antihistamines rapidly undergo complete biotransformation to active metabolites, which are as potent as, or even more potent than, the parent compound as histamine antagonists. Demethylastemizole and norastemizole block I_{Kr} (IC_{50} for demethylastemizole = 20 nmol/L), prolong the QT interval and induce EADs.[1,14] Terfenadine carboxylate is inactive in blocking I_{Kr}; thus, it should be evaluated as an antihistamine with less potential risk of causing torsade de pointes than terfenadine. Demethylastemizole is cleared very slowly from the plasma (terminal phase elimination half-life of ≈9 to 13 days),[17] which explains why abnormal QT prolongation and ventricular arrhythmias are likely to continue for long periods of time after discontinuing astemizole therapy.

3.2 Blockade of Other Cardiac Ion Channels

At concentrations that are much higher than those needed to block I_{Kr} (>1 μmol/L), all antihistamines can also block other ion currents (I_{Kto}, I_{K1}, I_{Na} and I_{Ca}).[1,16,18] Terfenadine is structurally related to the diphenylalkylamine class of L-type Ca^{2+} channel antagonists, and drug-induced I_{Ca} blockade may be responsible for smooth muscle relaxation, relief of bronchoconstriction and sinus and atrioventricular nodal arrhythmias.[18] The role of I_{K1} blockade is uncertain, since antihistamines had no effect on cardiac resting potential in multicellular preparations.[3,16] Because of their Na^+ channel antagonist properties, first generation antihistamines were used as local anaesthetics in individuals allergic to lidocaine and as class I antiarrhythmic agents. Na^+ channel antagonists exhibit potent proarrhythmic properties;[9] it is thus possible that antihistamine-induced I_{Na} blockade might explain severe conduction disturbances described in cases of astemizole cardiotoxicity[16] and facilitate the induction of cardiac arrhythmias under certain circumstances (i.e. myocardial ischaemia).

Studies of drug-channel interactions can be simplified by using a model in which channel clones are expressed in heterologous systems such as mammalian cell lines. This model system avoids contamination from other voltage-gated currents. We have analysed the effects of several antihistamines and their metabolites on the human cardiac K^+ channel (hKv1.5) stably expressed in L cells. This delayed rectifier is the counterpart of the I_{Kur} recorded in human atrial myocytes, which plays an important role in human atrial repolarisation.[6,7,19] Figure 2 shows that terfenadine, loratadine and its main metabolite, descarboxyethoxyloratadine (DCL), block hKv1.5 channels in a time-, voltage- and state-dependent manner, which may explain the supraventricular arrhythmias described with these drugs. They induced a decline in the current elicited by depolarisation and reduced the amplitude of the tail current recorded on return to –40mV. Blockade was voltage dependent, with a steep increase over the voltage range of channel opening (–30 to 0mV), suggesting that the drugs bind preferentially to the open state of the channel. At potentials positive to 0mV, blockade induced by terfenadine and DCL increased, while loratadine-induced blockade decreased with a more shallow voltage dependence. The voltage dependence of open channel blockade induced by terfenadine and DCL is the consequence of the effects of the transmembrane electrical field on the interaction between the drugs in their cationic form and the receptor at the channel level.[6,7,19] This explanation,

Fig. 2. Inhibition of human cardiac K^+ channel (hKv1.5) currents by terfenadine (left panel, 1 μmol/L), loratadine (middle panel, 1 μmol/L) and descarboxyethoxyloratadine (DCL; right panel, 50 μmol/L). **Row A:** superimposed current tracings evoked by 500 msec depolarisation from –80mV to +60mV and tail currents at –40mV in the absence (control) and in the presence of each drug. **Row B:** current-voltage relationships (500 msec isochronal) in the absence (control) and in the presence of each drug. **Row C:** voltage dependence of hKv1.5 inhibition expressed as normalised blockade ($I_{drug}/I_{control}$). Dotted line shows the voltage dependence of channel activation. δ = equivalent electrical distance. (After Delpón et al.,[6] Copyright 1997, Valenzuela et al.,[7] Copyright 1997, both reprinted with permission from Elsevier Science, and Caballero et al.,[19] with permission.)

however, cannot be applied to loratadine (pKa = 4.9), since at the intracellular pH it predominates in its uncharged form. It is conceivable that the affinity of the open channel receptor itself displays an intrinsic voltage dependence, even when additional binding to activated channel states that predominate below 0mV cannot be ruled out. This blockade may explain the supraventricular arrhythmias described with these drugs. In contrast, figure 3 shows that ebastine, its main metabolite carebastine and terfenadine carboxylate did not block hKv1.5 channels.[7]

Because the concentrations needed to block these channels are higher than plasma concentrations

Fig. 3. Effects of ebastine (left panel, 1 μmol/L), carebastine (middle panel, 3 μmol/L) and terfenadine carboxylate (TC; right panel, 3 μmol/L) on human cardiac K^+ channel (hKv1.5) currents. **Row A:** superimposed tracings evoked by 500 msec depolarisation from –80mV to +60mV in the absence (control) and in the presence of each drug. **Row B:** current-voltage relationships (500 msec isochronal) in the absence (control) and in the presence of each drug. (After Valenzuela et al.,[7] Copyright 1997, reprinted with permission from Elsevier Science.)

achieved clinically, it is tempting to suggest that the blockade of these currents may be clinically irrelevant. However, the large volume of distribution of some nonsedating antihistamines (terfenadine,[20] astemizole,[21] loratadine) results in cardiac concentrations that are much higher than corresponding plasma concentrations. Thus, it is possible that the blockade of these ion currents may be of clinical relevance for some antihistamines, particularly when prescribed with other drugs that block cardiac ion channels.

The extent to which an individual voltage-gated channel contributes to repolarisation is determined by different factors, including cell type (atrial *vs* ventricular, epicardium *vs* endocardium), heart rate, animal species and intrinsic regulation (sympathetic tone, hormones).[22] Furthermore, there are important differences between the functional properties of human cardiac K^+ currents and those from other mammalian species. Consequently, a classification of antihistamines based on the K^+ channels that each drug inhibits in animal species is nowadays unlikely to be useful clinically.

4. Clinical Implications

The recent reports of torsade de pointes and cardiac death associated with nonsedating antihistamines have raised questions regarding the risk versus benefit of these drugs. The scarcity of clinical reports of torsade de pointes, despite the widespread use of these antihistamines in otherwise healthy patients, suggests an idiosyncratic reaction. It has been suggested that patients who experience antihistamine-related torsade de pointes may have a subclinical genetic abnormality in the ion channels involved in cardiac repolarisation, or

in the genes involved in regulation of channel expression, which increases their susceptibility to drug-induced QT prolongation. It is also possible that mutant channels are not dysfunctional in themselves, but interact with the antihistamine in a manner distinct from drug interactions with wild-type channels.

A better understanding of the mechanisms of torsade de pointes and the identification of individuals in whom risk factors are present (table I) should allow physicians to anticipate and, therefore, avoid this potentially lethal complication. Antihistamines should be used with extreme caution in patients with severe hepatic dysfunction or in those who have been pretreated with drugs that inhibit oxidative CYP enzymes (CYP3A4) or prolong the QT interval. Unfortunately, despite extensive efforts to warn physicians and pharmacists, satisfactory awareness of the potential interactions between antihistamines and other drugs has not been achieved.[1] Furthermore, patients must be instructed to limit the dosage to that recommended in the manufacturer's labelling. However, even at clinically recommended doses, some antihistamines can cause torsade de pointes in patients with the congenital long QT syndrome[23] or with secondary forms of delayed repolarisation associated with coronary artery disease, hypothyroidism or electrolyte disorders, especially hypokalaemia or hypomagnesaemia.[1,14] Antihistamines are also included in certain combination products containing drugs that can potentiate the proarrhythmic risk. This is the case for α-adrenergic agonists used as decongestants, which prolong the QT interval[1,24] and enhance the development of EADs; however, the proarrhythmic risk of these widely prescribed combinations is unknown.

5. Future Developments

The development of new, safer, antihistamines is linked to a better understanding of their effects on the cellular mechanisms regulating human cardiac repolarisation. The cardiac electrophysiological effects of old and new antihistamines as well as their active metabolites on the QT interval and cardiac ion channels and their modulation by neurohumoral factors must be evaluated. Unfortunately, as recently reviewed, this information has not been described even for antihistamines that have been on the market for decades.[1] Finally, the recent identification of mutations in *HERG* as a cause of acquired and congenital forms of the long QT syndrome not only represents a major milestone in understanding the mechanism of drug-induced torsade de pointes, but offers the possibility of developing specific therapeutic approaches based on specific functional properties of mutant gene products.[8]

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