Cardiotoxicity of H1-antihistamines

Abstract
The H1-antihistamines are drugs that have been developed and marketed to treat noncardiovascular diseases and these drugs have been known to induce a number of untoward cardiovascular effects. This review summarizes current literature to evaluate the cardiotoxicity of H1-antihistamines.

Keywords: arrhythmia, cardiotoxicity, cardiovascular, H1-antihistamines, QT prolongation

Abbreviations: H1A, H1-antihistamines; hERG, human ether-a-go-go–related gene

Introduction
Today the H1-antihistamines (H1A) are among the most widely used drugs worldwide to treat various allergic diseases, for which its effectiveness has been proven, such as allergic rhinitis, conjunctivitis and urticaria.1 Also H1A are used for other purposes such as prevention/treatment of disorders related to activation of the vomiting centre and sedation.2 H1A act as inverse agonists that combine and stabilize with the inactive conformation of the H1 receptor, shifting the equilibrium to the inactive state. Through this mechanism of action, these compounds can regulate allergic inflammation.3

While sedation and antimuscarinic effects are the most frequent adverse drug reactions for H1A, cardiac toxicity represents a very rare but severe complication.4–9 First generation sedative antihistamines—e.g., diphenhydramine, which causes marked sedation, central nervous system dysfunction, and anticholinergic adverse effects—are still widely used in several countries,6–7 where they are a major cause of drug toxicity. Second generation H1A were introduced in the 1980s as non-sedative and specific H1A.1,3,4,6 However, after approximately 10 years of worldwide use, H1A such as astemizole and terfenadine, were found to cause prolonged QT interval in the surface electrocardiogram and were withdrawn from the market due to the risk of sudden cardiac death and ventricular tachyarrhythmia, associated with QT prolongation.1,4,6 It has prompted a reexamination of the possible cardiac adverse effects exerted by older compounds belonging to this therapeutic class of drugs.6

Clinical Evidence
There is a great amount of non-cardiovascular drugs that produce undesirable side effects in cardiovascular physiology, such as antibiotics9–10 and H1A.1,2,4,6,10 Many AH1 are available worldwide today (Table 1), and new types are developed nowadays.1,3,11 Several clinically useful drugs are able to antagonize the effects of histamine at the level of H1 receptors were developed in the fourth and fifth decades of the last century.1,3,12 These included chlorpheniramine, brompheniramine, hydroxyzine, and diphenhydramine. To improve selectivity for H1 histamine receptors and to minimize the well-known sedative effects of these “first generation” molecules, the so-called “second generation” H1A were introduced in the mid 1980s. Terfenadine was the first of these to be marketed, astemizole was the second of the newer non-sedating drugs to be marketed, and it has been widely prescribed, although less than terfenadine. Also loratadine and cetirizine have been available for several years; these drugs are also less sedating and have been approved for marketing.1,2,4,6,11,12 These two non-sedating H1A at doses three to six times higher than clinically recommended for treatment of allergic conditions failed to prolong QT intervals in normal subjects.6,11,12 The second generation H1A remaining in use are free from potential cardiac adverse effects.1,3 Third generation H1A are the active enantiomer (levocetirizine) or metabolite (desloratadine and fexofenadine) derivatives of second generation drugs. These drugs were intended to be more efficacies with fewer adverse drug reactions. However, there is little evidence for any advantage of levocetirizine or desloratadine, compared to cetirizine or loratadine, respectively.3 The terms third generation, new generation, or next generation have been used to market some new H1A; however, this designation should be reserved for clinically advantageous H1A designed with the use of molecular techniques that might be available in the future.13

In 1986, reports began to appear indicating that patients who took terfenadine or astemizole could develop a classical form of ventricular arrhythmia, Torsades de pointes. This caused that these drugs were withdrawn from the market.4,6,11,15 Older first generation H1A are widely sold in most countries as “over the counter” or prescribed medications and are frequently implicated in accidental or intentional poisoning. The issue of the potential cardiotoxicity of older antihistamines has been raised by recent studies. Some first generation H1A potentially cause dose-related cardiac adverse effects, including sinus tachycardia, reflex tachycardia, supraventricular arrhythmias, and after intentional large overdose, for example, diphenhydramine 0.5 to 1 g, prolongation of the QT interval with ventricular arrhythmias and Torsades de pointes has been documented.14 Therapeutic doses of diphenhydramine were also effective in lengthening cardiac repolarization in vivo in normal volunteers and in patients undergoing angioplasty.15 Arrhythmogenic properties in vivo have also been described for promethazine, pheneramine and chlorpheniramine (Table 1).6

Recently, Poluzzi et al.2 reported increased risk of ventricular tachyarrhythmia for current use of cizclyzine, dimetindene and ebastine; while cetirizine, fexofenadine and loratadine were in absence of high...
risk of ventricular tachyarrhythmia. Hydroxyzine, a sedative agent, which shares with cyclizine the molecular core (diphenyl-methyl piperazine), many receptor activities and some indications, recently received restrictions of use (i.e. limitations in daily dose and duration of exposure) by the European Medicine Agency for the proarrhythmic risk following pharmacovigilance findings, which confirmed evidence of potassium channel blocking properties. Serious cardiotoxic events occur very rarely during assumption of H1A; in a UK study involving approximately 200 000 people who received 500 000 prescriptions of five non-sedating H1A: acrivastine, astemizole, cetirizine, loratadine and terfenadine, it has been estimated that the absolute effect is quite low, requiring 57,000 prescriptions, or 5300 person-years of use, for one case to occur. Table 1 lists the H1A drugs that are available and summarizes the reported cardiotoxicity for some of them.

Table 1 Cardiotoxicity associated with the consumption of first- and second-generation antihistamines

| Generic name of H1A (Brand name) | Chemical class | Cardiotoxicity | Refs |
|----------------------------------|----------------|----------------|------|
| **First-generation**             |                |                |      |
| Doxepin (SINEQUAN)               | Tricyclic Dibenzoxepin | Yes | 20–22 |
| Carbinoxamine maleate (RONDEC, others) | Ethanolamines | ? | No reported |
| Clemastine fumarate (TAVIST, others) |                | Yes | No reported |
| Diphenhydramine (BENDRYL, NYTOL, UNISOM, SOMINEX, DIMEK, DAEDALON) |                | Yes (dose-dependent) | 14,15,25–30 |
| Dimenhydrinate (DRAMAMINE, others) |                | Yes | 40,31–33 |
| Pyrilamine maleate (POLY-HISTINE-D) | Ethylenediamines | Yes (overdose) | 32,33 |
| Triphenylamine (PBZ)             |                | ? | No reported |
| Chlorpheniramine maleate (CHLOR-TRIMEETON, others) | Alkylamines | Yes (overdose) | No reported |
| Brompheniramine maleate (BROMPHEN, others) |                | Yes (non clinical) | 39 |
| Hydroxyzine (ATARAX, VISTARIL, ATERAX, ALAMON, DURAX, EQUIPOSE, MASMORAN, ORGATRAX, PAXISTIL QUIES, TRAN-Q, TRANQUIZINE) | Piperazines | Yes | 16–18,40–45 |
| Cyclizine (MAREZINE)             |                | ? | No reported |
| Meclizine (ANTIVERT, others)     |                | ? | No reported |
| Promethazine (PHENERGAN, others) | Phenothiazines | Yes | 46,47 |
| Cyproheptadine (PERIACTIN)       | Piperidines | No | 42 |
| Phenindamine tartrate (NOLAHIST) |                | ? | No reported |
| **Second-generation**            |                |                |      |
| Acrivastine (SEMPREX-D)          | Alkylamine | ? | No reported |
| Cetirizine (ZYRTEC)              | Piperazine | No | 14,15 |
| Azelastine (ASTELIN)             | Phthalazinone | Yes | 52,53 |
| Levocabastine (LIVOSTIN)         | Piperidines | No | 53 |
| Loratadine (CLARITIN)            |                | No | 2,54–55 |
| Desloratadine (CLARINEX, AERIUS) |                | No | 56 |
| Ebastine (EBASTEL)               |                | Yes | 2 |
| Mizolastine (MIZOLLEN)           |                | No | 57–59 |
| Fexofenadine (ALLEGRA, TELFAST)  |                | Yes (one case reported) | 60,61 |

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Molecular target for H1A-induced cardiotoxicity

Cardiac toxicity of H1A does not occur through the H1 receptor, and is not a class effect. Rather, it is due to blockage of cardiac ion currents, such as potassium and sodium channel. The most important molecular mechanism of QT prolonging drugs has been shown to be the blockade of the delayed rectifier potassium channel (IKr), encoded by the human ether-a-go-go–related gene (hERG), which is located on chromosome 7. This can induce Torsades de pointes that it is a ventricular tachycardia associated with delayed cardiac repolarization that can manifest as a prolonged QT interval on the electrocardiogram and that may cause syncope, seizure, ventricular fibrillation, and sudden death.

Beyond hERG channel blockade, additional mechanisms can be involved in proarrhythmic activity of these drugs; for instance, sodium channel blockade by first generation H1A should be considered. Pastor et al. reported a case of Brugada syndrome unmasked by dimenhydrinate, hypothesising that sodium channel involvement was the basis for the observed event. Also antimuscarinic properties of some antihistamines may play a role in tachyarrhythmia occurrence: desloratadine, similarly to diphenhydramine, expresses high antimuscarinic activity on the heart, by resulting in a potential risk of pacemaker rhythm impairment, whereas loratadine and cetirizine showed lower affinity for cardiac muscarinic receptors.

More recently, Yun et al. also suggested a molecular mechanism involved in H1A-induced cardiovascular adverse effects other than hERG channel inhibition that are associated with p21 (Cdc42/Rac)-activated kinase 1 (pak1) mRNA expression and function. The achievements of cellular electrophysiology and molecular genetics are shedding some light on the potential cardiotoxicity of H1A, an issue that might be crucial in specific therapeutic and toxicological settings.

Factors contributing to risk of cardiotoxicity of H1A

Importantly, it has become apparent that the QT interval, despite its obvious importance, is but 1 of several risk factors of patients using H1A with different indications and to genetic predispositions, that must be considered in order to assess a patient’s risk profile for Torsades de pointes. Numerous studies suggest that in order for a strategy to have an acceptable level of predictive accuracy and be cost effective, it must include consideration of those risk factors that are patient-specific, drug-specific, and clinical scenario-specific.

Patient-specific risk factors for drug-induced Torsades de pointes are the same factors that are known to be associated with an increase in the QT interval, that is, female sex, bradycardia, hypokalemia, hypomagnesemia, hypocalcemia, diuretic agent use, hypothermia, and history of heart disease. As discussed earlier, the common feature of H1A that cause Torsades de pointes is their ability to block hERG channels and to prolong the QT interval.

Most likely, the interindividual variability in drug sensitivity and the variable influence of factors that affect each patient’s drug exposure (e.g., dose, drug metabolism, route of administration, and so forth) reduce the predictive accuracy of such ranking to levels that lack clinical utility. For example, terfenadine and astemizole have very high hERG blocking potency but are usually extensively metabolized so that it is unusual for them to reach blood levels that can cause Torsades de pointes (i.e., only when their metabolism had been inhibited or impaired).

Analyses of case series of Torsades de pointes due to a specific drug reveal that the great majority of cases fall into certain categories of drug use that are influenced by the patients’ medical condition. Many of the patients in these reports had been successfully treated with the offending drug for extended periods of time, but developed Torsades de pointes after a change had occurred in their clinical condition or in the way it was managed. Many of these changes could have further reduced the patient’s repolarization reserve and caused excessive QT prolongation. The concept of repolarization reserve by Roden maintains that every person has a physiological cardiac repolarization reserve, which is genetically determined and compensates for any factor (e.g., drugs) that might either decrease repolarizing or increase depolarizing currents during the action potential. This last aspect is currently under intense scrutiny, with a growing awareness of the importance of genome-wide association studies, in addition to the already consolidated focus on single candidate genes (e.g. those encoding specific ion channels). So far, reduction of repolarisation reserve, due to specific polymorphisms, is supposed to be a possible mechanism predisposing to drug-induced QT prolongation.

Another factor in H1A safety is the dependence on drug–drug interference at the level of metabolism, the lack of significant hepatic metabolism probably contributes to the freedom from significant cardiotoxic potential shown by some other second generation H1A, such as desloratadine, cetirizine, levocetirizine, and acrivastine. Beside the clinical conditions causing an increase in the H1A plasma levels well above therapeutic values, it should be emphasized that cases have also been described in which the arrhythmic episodes occurred at “therapeutic” drug concentrations.

Therefore, physicians before prescribing an H1A should be aware of the following points. If the patient has any form of cardiac disease, an H1A with minimal cardiac effects should be used. If the patient using other drugs to induced QT prolongation and Torsades de pointes such as macrolides, opiates, imidazolic compounds, antipsychotic, antimalarial or antimigraine drugs, the prescription of H1A should be cautious or avoided. If the patient shows any risk factor, such as special diet (grapefruit juice), hepatic disease, electrolyte disturbance, and use of anti-arrhythmic drugs with potential of extending QT interval, prescription of H1A should be preceded and followed by a cardiologist.

Conclusion

H1A are widely used, many of them are nonprescribed over the counter medications and well-known drugs by public. However, potentially dangerous cardiac unwanted effects of these drugs should be recognized by the general public. Patients at risk of Torsades de pointes, such as those with liver disease, congenital prolongation of the QT interval, electrolyte disturbance, arrhythmias, or other illness requiring drugs that prolong QT interval, should not be given H1A that are capable of prolonging repolarization. When patients take massive overdosage of an H1A, it is very likely that the drugs could alter cardiac conduction, contractility, and/or repolarization, depending on the agent and the magnitude of the overdose. In the next few years
the perception of drug-induced cardiovascular toxicity might easily change because of the approval of safer drugs or refinements of techniques for predicting, managing, or preventing such toxicity.

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Conflict of interest

The authors declare that there is no conflict of interest.

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