Review paper

Cardiovascular safety of antihistamines

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Abstract

Histamine is a mediator, which increases the permeability of capillaries during the early phase of allergic reaction, causes smooth muscle contraction of bronchi and stimulates mucous glands in the nasal cavity. Antihistamines are the basis of symptomatic treatment in the majority of allergic diseases, especially allergic rhinitis, allergic conjunctivitis, urticaria and anaphylaxis. The cardiotoxic effects of the two withdrawn drugs, terfenadine and astemizole, were manifested by prolonged QT intervals and triggering torsades de pointes (TdP) caused by blockade of the 'rapid' I_{Kr} potassium channels. These phenomena, however, are not a class effect. This review deals with a new generation of antihistamine drugs in the context of QT interval prolongation risk.

Key words: histamine, H1 receptor, antihistamines, QT interval, torsades de pointes.

Histamine is a mediator abundantly released by mast cells. It covers a broad spectrum of biological activities executed through the pathways of H1, H2, H3 (present mainly in the nervous tissues), and H4 receptors, as well as through the intracellular Hic receptor [1, 2]. The symptoms of allergic response are a result of histamine acting on H1 receptors. In the early IgE-dependent allergic reaction, along with other mediators, histamine increases general permeability of capillaries and arterioles and permeability of vessels to plasma proteins. It causes smooth muscle contraction of bronchi and stimulates mucous glands in the nasal cavity [2]. The mediators of allergic response are virtually the same in different tissues, yet clinical symptoms are specific to particular organs. Skin develops hives and erythema, lower respiratory tracts induce bronchoconstriction, dyspnea, wheezing and coughing, while nasal mucous membranes respond through pruritus, sneezing, production of aqueous secretion and nasal congestion. Stimulation of H1 receptors within the cardiovascular system results in the constriction of coronary blood vessels and induces a positive chronotropic effect, while the stimulation of H3 receptors is negatively chronotropic [3]. Additionally, histamine may inhibit β1-adrenergic receptors within the heart muscle.

Antihistamines are the logical basis of symptomatic treatment in the majority of allergic diseases, especially allergic rhinitis, allergic conjunctivitis, urticaria and anaphylaxis. They act on a receptor level by competing for H1 receptor sites with histamine (competitive antagonism). Once bonded to inactive receptors, they stabilize them in their inactive form, thus preventing activation by their natural agonist – histamine (inverse agonism) [1]. On top of that, antihistamines show anti-inflammatory and anti-allergic action that is not receptor related, e.g. through the inhibition of mast cell degranulation, eosinophil and neutrophil chemotaxis and down-regulation of nuclear factor κB (NFκB) activity [1]. Novel antihistamine drugs, such as rupatadine, additionally block the platelet-activating factor (PAF) receptor, which plays an important role in allergic response, by inducing bronchoconstriction and bronchial hyperresponsiveness, increased permeability of vessels and neutrophil chemotaxis [1, 4]. Early antihistamines (first-generation – Table 1), introduced in the 1940s, affect also dopaminergic, serotonergic and cholinergic receptors, inducing multiple side-effects, such as sedation. The advantage of newer antihistamines (second – and third-generation) is the selective H1 binding and their anti-inflammatory effect. The newest third-generation antihistamines are either metabolites or isomers of the second-generation drugs (Table 1).

A certain level of concern regarding the safety of antihistamines was brought up by cardiotoxic effects of the first two second-generation antihistamines – terfenadine and astemizole. These effects were primarily manifested

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by the appearance of the acquired, drug-induced long QT syndrome (LQTS). This phenomenon is caused by blockade of the 'rapid' I_{Kr} potassium channel, encoded by the human Ether-à-go-go-Related Gene (hERG) [5, 6]. The channel is activated during phase 3 of the action potential – repolarization. Action potential is prolonged, once the channels are blocked. In such event, surface electrocardiogram (ECG) displays long QT intervals, while the patient is more vulnerable to the particularly threatening torsades de pointes that might develop into ventricular fibrillation and eventually death. Potassium channel blockade most likely results from the characteristic structural properties of particular drugs and their polarity [3, 5].

The assessment of QT interval prolongation is usually straightforward and requires a surface electrocardiogram (ECG) – Table 2. Notably, drug-induced prolongation of QT interval may be detected during treatment with the use of control electrocardiograms.

The first case of torsades de pointes, regarding a 16-year-old female and resulting from an ingestion of 20 astemizole tablets (200 mg), which had been prescribed 10 mg daily due to allergic rhinitis, was presented by Craft in 1986 [7]. A similar case of terfenadine overdose in a 21-year-old female was described by Davies *et al.* in 1989 [8]. Other case studies, concerning cardiotoxic side-effects of overdosed astemizole or terfenadine, followed shortly after [9, 10].

As a result of these disturbing data, having carefully analyzed over 20 cases of fainting, ventricular tachycardia, torsades de pointes and cardiac arrests that followed administration of astemizole or terfenadine, the Food and Drug Administration (FDA) published a warning for physicians describing the conditions of usage of these medicines [9]. It was established that torsades de pointes might appear not only in cases of overdose [11], but also in the presence of other factors up-regulating the concentration of these drugs in the serum. Most of such cases were related to astemizole or terfenadine metabolism disorders. Some antihistamines, e.g. terfenadine, astemizole, levocetirizine or rupatadine are metabolized in the liver by the cytochrome P450 enzyme complex – the CYP3A4 isoenzyme, while loratadine is also metabolized by the CYP2D6 isoenzyme [3]. Certain metabolites, e.g. cetirizine, desloratadine and bilastine, are not metabolized in the liver or their liver metabolism is clinically insignificant. A simultaneous use of medicines which inhibit the CYP3A4 isoenzyme results in an elevated concentration of these antihistamines in the serum, leading to an increased risk of potential toxic side-effects. Therefore, the use of these antihistamines was not recommended in patients with hepatic disorders or inherited long QT syndrome, similarly to their combined administration with other QT interval prolonging drugs or CYP3A4 isoenzyme inhibitors, including macrolides, itraconazole and ketoconazole [3, 12]. Despite these warnings, new case-studies appeared describing unrecommended combined use of those drugs [13]. Additionally, QT interval prolongation was found in people drinking grapefruit juice combined with other medicines [9]. This might demystify the unexplained arrhythmia cases reported to the Food and Drug Administration (FDA) that had appeared with no apparent predisposing factors. New research suggests that some arrhythmia cases, which were related to terfenadine use, were in fact cases of the life-threatening ventricular tachycardia (other than torsades de pointes), caused by decreased conductivity, due to blocked sodium channels [14]. Astemizole was withdrawn from the market in Europe and the United States in 1997, while terfenadine, which was substituted for its metabolite – fexofenadine, was discontinued in 1999 [15].

Due to cardiotoxicity of astemizole and terfenadine, much attention was paid to the safety of other antihistamines. Furthermore, the assessment of novel drugs (bilastine, rupatadine, levocetirizine) was performed in accordance with the precise E14 regulations approved by the ICH (International Conference of Harmonization of Technical Requirements for Registration of Pharma-

Table 1. Generations of antihistamines

First-generation	Diphenhydramine, clemastine, triprolidine, hydroxyzine, cyproheptadine, promethazine, antazoline, dimetindene, ketotifen
Second-generation	Terfenadine, astemizole – withdrawn Loratadine, ebastine, cetirizine, rupatadine, mizolastine, emedastine, azelastine, bilastine
Third-generation	Desloratadine – metabolite of loratadine Fexofenadine – metabolite of terfenadine Levocetirizine – enantiomer of cetirizine

Table 2. QT interval measurement

The QT interval measurement is performed from the beginning of the earliest Q wave (or the R wave, if the Q wave is missing) to the end of the T wave, excluding the U wave, if present. A mean result of 3–5 measurements is advisable.
Due to the fact that QT interval is dependent on the heart rate, it is recommended to use correction formulas. The most common is the Bazett's formula, in which the QT interval is divided by the square root of the RR interval (measured before the QT interval). Both intervals must be measured in the same units of time.
The correct value is 430 ms for adult males, 450 ms for adult females and 440 ms for children. Values above 450 ms in adult males, 470 ms in adult females and 460 ms in children are considered as substantially prolonged.

ceuticals for Human Use). These regulations concern the assessment methods of proarrhythmic potential of non-antiarrhythmic drugs. Some of the most important representatives of antihistamines are noteworthy:

- Diphenhydramine – the proarrhythmic effect, due to the influence on potassium channels, was reported while administering medically overdosed diphenhydramine [3, 16]. An increased repolarization time and T wave disturbances were also reported in the case of another first-generation antihistamine – hydroxyzine [3, 17, 18].
- Fexofenadine – this terfenadine metabolite is minimally metabolized. Although a case of prolonged QT interval and ventricular tachycardia while administering fexofenadine had been reported [19], the studies that followed did not confirm its negative effects on QT interval and heart rhythm, neither in high doses nor combined with ketoconazole or erythromycin [20].
- Ebastine – the mechanism of action is based on its active metabolite – carebastine. Although experimental studies did reveal prolonged QT intervals in doses far greater than the ones necessary to block H1 receptor [21], the clinical studies did not confirm its substantial prolongation in humans. Arrhythmia was not observed, even in patients equipped with a Holter monitor [22–24]. Combined administration of ebastine with ketoconazole or erythromycin resulted in its increased concentration in the serum and a slight QT interval prolongation, yet with no clinical significance whatsoever [23]. Precaution is recommended in the case of patients with prolonged QT interval, hypokalemia and in cases of combined use with QT interval prolonging drugs or isoenzyme CYP3A4 influencing therapeutics [25]. Ebastine is unavailable in Poland.
- Cetirizine – it is excreted in the urine in 70% and undergoes minute, clinically insignificant metabolism in the liver. Experimental studies [26, 27] and human trials did not confirm its effect on potassium channels, nor its properties to induce torsades de pointes [26, 28]. Hekkala *et al.* [26] assessed the use of cetirizine in patients with inherited type 1 and type 2 long QT syndrome. They did not observe prolonged QT intervals, neither during rest, nor after physical exertion, having administered a therapeutic dose of 10 mg to the patients or 50 mg doses to the healthy volunteers. Levocetirizine in an enantiomer of cetirizine. A study in accordance with E14 ICH regulations did not reveal its effect on repolarization in either therapeutic or higher doses [29].
- Loratadine – is metabolized by CYP3A4 and CYP2D6 isoenzymes, thus interactions with their inhibitors are possible. No substantial influence on the prolongation of QT intervals or ventricular arrhythmia was shown [3, 30]. Taglialatela *et al.* [27] described a potential experimental possibility of potassium channel blockade and QT prolongation, yet with the use of doses far higher than therapeutic ones. Desloratadine is a metabolite of loratadine. No QT interval prolongation was found as a result of administration of desloratadine [25].
- Mizolastine – is structurally similar to astemizole. When used experimentally, in higher than therapeutic doses, it blocked the potassium channels to some degree [31]. Human trials, however, did not result in QT interval changes, neither with normal doses, nor overdosed [32, 33]. Mizolastine is unavailable in Poland.
- Rupatadine – blocks both H1 and PAF receptors [34]. It binds to potassium channels only in very high concentrations, 400× higher than the ones achieved with the 20 mg dose [34]. It is metabolized by the CYP3A4 isoenzyme, thus its concentration in the serum is increased during combined use with CYP3A4 inhibitors, yet it has no significant effect on the QT interval prolongation [35, 36]. Studies on healthy volunteers did not reveal any significant QT prolongation, neither with therapeutic doses, nor while being overdosed 10-fold [4, 36]. Nonetheless, precaution is recommended in the case of rupatadine use in combination with isoenzyme CYP3A4 inhibitors, in patients with prolonged QT interval, ongoing hypokalemia or in other cases that might result in arrhythmia (such as clinically significant bradycardia or acute myocardial ischemia) [25].
- Bilastine – it is characterized by high selectivity and affinity towards H1 receptors. It does not show significant activity towards a group of 30 other receptors, including serotonergic, bradykinin, leukotriene, muscarinic, calcium-sensing, α1 and β2 adrenergic, as well as H2 and H3 receptors [37]. It is excreted unchanged in almost 95%, it is not metabolized in the liver and does not affect the P450 cytochrome. Due to these advantages, bilastine shows high therapeutic effectiveness with a rapid onset and a long clinical action as well as high reduction of side-effects. A randomized study on 30 healthy volunteers, in accordance with the E14 ICH regulations, revealed that bilastine does not significantly prolong the QT interval and does not cause arrhythmia, when used in therapeutic doses or overdosed 5× [38–41]. Although QT intervals were prolonged in the group of patients that were simultaneously taking bilastine and ketoconazole, this phenomenon was supposedly caused by the anti-fungal drug itself, because the QT prolongation was observed only when ketoconazole reached its maximum concentration [38]. On top of that, these patients showed lowered bilastine concentrations, compared to a group of patients that were overdosed (100 mg) and yet did not experience any prolonged QT intervals. Clinical studies on healthy volunteers revealed that high doses of 10× to 11× (220 mg one-time or 200 mg daily for 7 days) did result in a higher incidence of side-effects, yet without any significant QT interval prolongation [38].

The aforementioned studies reveal that the triggering of life-threatening arrhythmia is not a class effect.

This phenomenon concerns mainly two antihistamines (i.e. terfenadine and astemizole) and is proportional to the level of potassium channel blockade [3]. Therefore, it does not depend on the primary affinity towards H1 receptors.

Interestingly, Turkish researchers, Erdogan *et al.*, assuming that histamine released from mast cells during acute myocardial infarction causes constriction of coronary vessels, carried out a study, in which loratadine 10 mg daily was added to the standard treatment of acute myocardial infarction [42]. They thought that the antihistamine property of the drug could inhibit the negative effect of histamine in the case of insufficiency of vasodilating factors. They reported better results in cardiac stress tests in patients taking loratadine compared to conventionally treated patients. The hypothesis claiming that mast cells and histamine play a role in acute coronary syndromes attracted more scientific attention. Reid *et al.* reported that angiotensin II and histamine, which are released by mast cells during heart attack, activate AT1 and histamine H3 receptors, while the AT1 activation has a proarrhythmic effect and the H3 activation is cardioprotective [43]. Thus, the researchers suggested that acting upon histamine receptors might create a novel therapeutic option in the future. Furthermore, Matsumori *et al.* reported a decrease in myocardial necrosis area and lowered levels of inflammatory cytokines and metalloprotease-2 in mice with viral myocarditis treated with cetirizine [44]. Undoubtedly, the apparent positive effects of antihistamines on the circulatory system require further investigation.

Conclusions

Effects of potassium channel blockade and QT interval prolongation are not a class effect, but result from the action of only a few antihistamine drugs – arrhythmias with dramatic effects were observed only in the case of the withdrawn therapeutics – terfenadine and astemizole. Such phenomena are potentially manifested only in the cases of high overdose far beyond the suggested therapeutic levels. Furthermore, in the vast majority of these cases the results had no arrhythmogenic consequences. There are certain groups of patients, especially the ones with inherited long QT syndrome, the elderly and patients with cardiovascular diseases, who require special attention, once they are to be treated with any of the vast majority of antihistamines. In such cases, patients should be warned not to overdose their prescribed antihistamines and not to combine them with CYP3A4 inhibitors (e.g. anti-fungal drugs and macrolides), nor with any drugs prolonging QT intervals. The optimal way to avoid these problems is to use antihistamines with the highest level of cardiovascular safety, e.g. bilastine, which does not affect the CYP3A4 isoenzyme, nor the QT interval, even when overdosed.

Conflict of interest

Anna Olasińska-Wiśniewska – lecture honorarium from Berlin-Chemie.

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