European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2001; 5: 139-142

Antihistamines and the torsade de point in children with allergic rhinitis

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Abstract. – **Allergic rhinitis (AR) is a very common disease, occurring in approximately 10% of children and up to 20% of adolescents. It is often underdiagnosed and its importance as a cause of morbidity is also underestimated, especially in asthmatic children. It has been estimated that 75% of asthmatic children suffer from AR, and its prevalence has increased during the last years, due to changes in environmental factors. AR may be a cause of serious discomfort for the child as well as for the family.**

AR may cause several complication, including serous otitis media, abnormal facial development with orthodontic problems, eustachian tube dysfunction and sinusitis. The frequent association of paranasal sinusitis in children with asthma has been observed and sinusitis has been considered a contributing factor in bronchial asthma Second-generation antihistamines are the golden therapy for AR. However, reports of potentially life-threatening dysrhythmias, specifically torsades de pointes, were described.

In conclusion, we comment the in vitro inhibition of several ion channels, in particular predisposing the heart to dysrhythmias by terfenadine and astemizole. In this paper we examine recent reports on safety of both cetirizine and loratadine.

Key Words:

Allergic rhinitis, Cetirizine, Loratadine, Terfenadine, astemizole, Torsade de point, Cardiovascular adverse effects, Safety of antihistamines in children.

Introduction

Allergic rhinitis (AR) is a very common disease in children, often underdiagnosed and with underestimated complications[1]. The therapy of AR is based on the use of second-generation antihistamines, acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, levocabastine, loratadine, mizolastine and oxatomide which compared to "classic" first-generation antihistamines express an "antiallergic" activity[2]. Above all, these drugs fail to share the adverse central nervous system (CNS) effects which made controversial the use of first-generation antihistamines. They cause fewer undesirable CNS actions, since do not penetrate the blood-brain barrier, nor cause significantly less learning impairment in children[3,4].

Recently, cardiovascular side effects induced by both terfenadine and astemizole have been reported, that is the ability of blocking in vitro the delayed outward rectifier potassium channel in the myocardium, predisposing the heart to dysrhythmias and to an ECG pattern (prolongation of the QT interval) known as torsades de pointes)[5,6]. Terfenadine has been withdrawn from France markets in 1998 even if the risk of adverse reactions is uncommon and we stress: especially in children[6]. In 25 patients who complained of adverse reactions, among whom a 16-year old boy due to intentional overdose, the mean age was 53,3 years[7].

Astemizole's onset of action occurs within 2 days and the therapeutic activity may need 4 days to reach a steady state[8]. Therefore we hypothesize that untoward effects could go back to its long-lasting delay in reaching therapeutic concentrations. It may be that some doctors could be tempted to prescribe higher initial doses, with a further increase in serum levels[6]. Concerning the variables contraindicating terfenadine and astemizole prescription (Table I)[8], children may be at risk due to a coprescription of macrolide antibacterials, antifungals, etc, especially if they are cardiopathic or hepatopathic, just following assumption of grapefruit juice, whereas the risks related to acrivastine,

Table I. Risk factors possibly associated with cardiovascular adverse effects of astemizole in children.

Concomitant medications involving liver cytochrome P450 metabolism
Azole antifungal agents: ketoconazole, itraconozole
Macrolide antibiotics: erythromycin
Cimetidine
Natural flavonoids: grapefruit juice
Overdose
Heart abnormalities
Prolonged QT interval
Ischemic heart disease
Congestive heart failure
Anti-arrhitmic medications: qinidina
Metabolic abnormalities
Hypokalemia: use of diuretics
Hypomagnesemia
Anorexia, fluid protein diet
Severe liver disease

Modified from reference 8.

cetirizine and loratadine are even lower[9,10], limited to 1-13 $\times$ 10^6 defined daily doses (DDDs) sold[5].

Torsade de point

After approximately 10 years of widespread clinical use[2], disturbing reports of potentially life-threatening dysrhythmias, specifically torsades de pointes, were described. Both terfenadine and astemizole have been shown *in vitro* to inhibit several ion channels, and in particular the delayed outward rectifier potassium channel in the myocardium, predisposing the heart to dysrhythmias. On the contrary, loratadine, fexofenadine, mizolastine, ebastine, azelastine, acrivastine and cetirizine have been shown to be efficacious with few adverse events[5] including no clinically relevant cytochrome P450 mediated metabolic-based drug-drug interactions or QT interval prolongation/cardiac dysrhythmias[11].

A recent study has investigated the cardiac effects of the H1-receptor antagonists terfenadine, astemizole, loratadine and cetirizine, used in recommended doses, concomitantly or not with the antibiotic erythromycin in 80 atopic children aged 5 to 12 years, all suffering from AR and with skin prick tests positive to Der p, the assumption of astemizole, cetirizine, loratadine and terfenadine administered with or without erythromycin to atopic children in recommended doses did not induce cardiotoxic effects, and the increase in QT interval, caused by terfenadine, was no more statistically significant after correction by the Bazzett's equation[6].

In an elegant study, rabbit ventricles were perfused with either cetirizine or astemizole. Cetirizine produced a mild biphasic electrocardiographic QT interval prolongation and was associated with early after depolarizations, but not with torsades de pointes. Astemizole lengthened QT intervals, and at high concentration (30 microM) induced torsades de pointes in 10 of 11 hearts These findings are consistent with previously reported repolarizing current inhibition by cetirizine, but may additionally indicate "compensatory" inhibition of inward currents at higher concentrations. By contrast, astemizole-induced changes are consistent with unopposed repolarizing current inhibition[12].

In a double-blind, placebo-controlled study in preparation we investigated the preventive efficacy of astemizole in 21 children aged 6-12 years with pollen-induced asthma and no personal history of cardiac disease or hepatic dysfunction, showing that astemizole with statistically significant differences reduced the asthma severity, cough, and bronchodilator usage during the pollen season with no adverse effects. At each follow-up visit the frequency, severity and relationship to the study drug of possible adverse experiences; eg somnolence, dry mouth and gastrointestinal complaints were recorded. The results confirm that astemizole is an effective and safe drug for AR management in children.

Conclusion

The negative influence of several environmental conditions seems to be more important for children with a family history of allergic diseases, thus stressing that environmental factors play a crucial role in children with a genetic propensity for allergic disease[13] (Figure 1).

There is no doubt that antihistamines have been the mainstay of treatment of AR and they still remain one of the most effective treatment for AR[2]. The new generation of non sedative specific H1 receptor antagonists

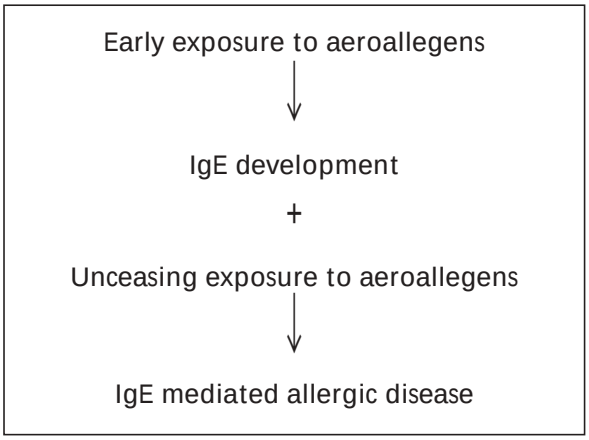

Figure 1. Sequence of events leading to allergic disease.

with reduced or no side effects has catapulted antihistamines to the forefront among antirhinitic drugs[2].

Delgado et al study[6] was criticized because the children received astemizole concomitantly with erythromycin[8], however we suggest that it is sufficient to contraindicate the association of both drugs, as it is stated in the product labeling[14], and we stress that astemizole only at high concentration (30 microM) induces torsades de pointes[12].

Ingestion of excessive doses of astemizole, as previously alluded to requires immediate medical attention. The drug needs only be taken once daily, and if it is occasionally forgotten, there seems to be no alteration to its efficacy, thanks to its long half-life (4 days). Children who accidentally ingest excessive doses of this compound may usually be adequately managed at home. However, patients ingesting large amounts (approximately > 3 to 4 times the normal therapeutic daily dose) should receive medical attention. These children should be monitored for 2 to 3 hours after the ingestion and children ingesting cetirizine should be advised about the potential for sedation. Although underreporting may have occurred, these adverse effects are rare, considering the millions of patient days of astemizole use, also on a nonprescription basis in several cases[15], that is 0.08 per 10^6 DDDs sold[5].

Cetirizine has represented the main choice for its efficacy and safety[16] and had the lowest rate of reports per 10^6 DDDs sold for total rate and rhythm disorders, that is around 0.,03 per 10^6 DDDs sold[5]. During the last year, we have prescribed the drug to hundreds of atopic children, regularly controlled every 3 to 6 months, and adverse effects have never been reported. However, loratadine 0.,013 per 10^6 DDDs sold[5] and fexofenadine were found to be associated with a lower incidence of sedation than acrivastine and cetirizine. In particular, cetirizine was 3.5-fold more likely and acrivastine 2.8-fold more likely to result in reports of sedation. This is why we prescribe acrivastine and cetirizine for evening assumption.

The dosage of the above antihistamines are reported in Table II[18]. Our preference for cetirizine and loratadine depend on their formulation on drops and syrup, respectively, obviously preferred by younger children.

Table II. Pediatric dosages of oral antihistamines.

Antihistamine	*Usual pediatric dosage*
Acrivastine (children aged > 12 years)	8 mg PO TID
Astemizole	0,2 mg/kg/die PO
Azelastine	1 spray BID
Cetirizine (tablet, drops)	0,2 mg/kg/die PO
Fexofenadine (children aged > 12 years)	120 mg/die PO*
Levocabastine	1 to 2 sprays BID
Loratadine (tablet, syrup)	0,2 mg/kg/die PO**
Oxatomide	1 mg/kg/die PO

PO = per os, BID = bis in die, TID = ter in die.
* single dose or in two divided doses, ** or for ages 2-12 years ≤ 30 kg body weigth 5 ml/die, or > 30 kg body weigth 10 ml/die in single dose.
Modified from reference 19.

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