Loratadine Produces Antihistamine Activity without Adverse CNS, ECG or Cardiovascular Effects in Guinea Pigs

Comparative Studies with Terfenadine and Sedating Antihistamines

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Sedation limits the antiallergy utility of classical H₁ antihistamines, while newer antihistamines are nonsedating. Loratadine and terfenadine represent prototypes of a new class of antihistamines that are devoid of central sedative effects [1-3]. By contrast, classical antihistamines such as diphenhydramine and promethazine induce sedation and drowsiness in humans, and exhibit significant anticholinergic side effects.

Recent reports of serious ventricular arrhythmias associated with the nonsedating antihistamines terfenadine [4] and astemizole [5], led the FDA to require labeling changes to identify risk factors associated with these arrhythmias. In the case of terfenadine, the arrhythmogenic cardiac toxicity is associated with high concentrations of the parent drug. Drugs that interfere with first-pass hepatic metabolism, such as the macrolide antibiotics and ketoconazole, can lead to dangerously high plasma levels of terfenadine, which have been shown to elicit torsade de pointes, a ventricular dysfunction that is potentially fatal. Torsade de pointes is a ventricular arrhythmia characterized by a prolongation of the QTc interval and twisting of the ECG wave form [6]. Drug-induced torsade de pointes in humans occurs secondary to a decrease in heart rate and a prolongation of the QTc interval (value > 550 ms) [7].

The mechanism underlying the cardiotoxicity of terfenadine appears to be blockade of rectifying potassium channels [8]. Due to the cardiotoxicity associated with terfenadine, and more recently astemizole, questions have also been raised regarding whether torsade-type arrhythmias can also occur with the newer agents such as loratadine. Although an extensive clinical data base with

loratadine indicates that this is not a problem, an animal model that could predict these adverse cardiovascular events is needed.

The goals of the present study were (1) to determine whether H₁ antihistamines produce a decrease in EEG activity in the guinea pig that is predictive of CNS-depressant

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liability, (2) to determine the relationship between the drug dose producing CNS effects and peripheral anti-H₁ activity, and (3) to compare the cardiovascular and ECG effects of loratadine and terfenadine. To perform these studies, we measured EEG and ECG activity in the anesthetized guinea pig. Diphenhydramine and promethazine were used as the standard sedating antihistamines for the EEG studies. The class Ia antiarrhythmic drug quinidine, which is known to produce torsade de pointes in humans [9] was used as a standard in the ECG studies.

To establish a quantitative experimental model for assessing the sedating potential, we used a model of CNS depression that responds to antihistamines in accord with their level of sedation in humans, using cortical EEG in guinea pigs. Drugs were administered intravenously (i.v.) to anesthetized guinea pigs and the integrated amplitude of the EEG signal was recorded. A comparison was made between the dose that depressed EEG activity (CNS effect) and the dose that inhibited histamine bronchospasm (anti-H₁ effect). Diphenhydramine and promethazine depressed EEG at doses between 0.6- and 2.0-fold their anti-H₁ doses. In contrast, loratadine had no depressant activity at 100 mg/kg, which was > 100-fold its anti-H₁ ED₅₀ (0.58 mg/kg). We were unable to study the CNS effects of terfenadine because it produced cardiovascular collapse at 10 mg/kg i.v.

The ECG effects of loratadine (30 and 100 mg/kg) and terfenadine (10 mg/kg) were also evaluated. Loratadine did not produce adverse cardiovascular effects, nor did it alter ECG activity. In contrast, terfenadine at 10 mg/kg, i.v., exhibited significant arrhythmogenic activity and produced prolongation of the QTc interval up to > 500 ms, severe hypotension, bradycardia, and disruptions of the PR interval. Furthermore, this dose produced a torsade-de-pointes-like syndrome, characterized by a twisting of the ECG wave. Quinidine (50 mg/kg) also produced a prolongation of the

QTc interval, bradycardia, hypotension and twisting of the ECG wave. The vehicles used in these studies, mefloquine and DMSO, did not affect cardiovascular parameters.

The adverse ECG and cardiovascular effects of terfenadine were observed at doses below its antihistamine activity. Specifically, the morphological profile revealed a torsade-de-pointes-like effect characterized by twisting of the QRS wave (twisting of the points). The degree of QTc prolongation increased throughout the course of the experiment, with some animals degenerating into ventricular fibrillation. The present findings represent the first demonstration of a terfenadine-induced torsade-de-pointes-like effect in an in vivo model and represents a valuable tool for studying the mechanism underlying drug-induced torsade-de-pointes-type ventricular arrhythmias. The effects of terfenadine in this experimental model closely resemble the qualitative and quantitative ECG changes seen in terfenadine-induced torsade de pointes in humans.

In a separate set of experiments conducted to determine loratadine plasma levels after i.v. administration, the doses of loratadine studied (30 and 100 mg/kg) produced plasma levels of loratadine and its primary metabolite, descarboeth-oxylopratadine that were several orders of magnitude greater than levels needed for biological activity in humans.

In conclusion, the sedative liability of the H₁ antihistamines (from greatest to least sedating) is promethazine – diphenhydramine >> loratadine = placebo. Furthermore, the present studies show that loratadine provides significant antihistamine activity at doses that are completely devoid of ECG and cardiovascular side effects. In contrast, terfenadine produced a myriad of side effects including ECG disturbances characterized by twisting of the ECG (torsade-de-pointes-like effect), QTc prolongation, hypotension and bradycardia.

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