

Use of Second Generation H₁ Antihistamines in Special Situations

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■ Resumen

Los fármacos antihistamínicos son una de las clases terapéuticas más utilizadas a nivel mundial, en todas las edades y en múltiples situaciones. Aunque en general presentan un perfil de seguridad bueno, solo los fármacos más recientes (los antihistamínicos de segunda generación) han sido estudiados específicamente en cuanto a los aspectos de seguridad más relevantes. Dada la variedad de fármacos antihistamínicos, no deben considerarse todos iguales a la hora de su indicación en diferentes situaciones clínicas especiales, en las que debe valorarse la experiencia clínica documentada en cada caso o, en ausencia de esta, las características particulares farmacológicas de cada molécula para su indicación en estas situaciones especiales.

En general, hay pocos estudios clínicos publicados en grupos de pacientes con insuficiencia renal o hepática, con pluripatología concomitante (como la patología cardíaca), en edades extremas (pediatría o ancianos) y en periodos naturales como son el embarazo o la lactancia, pero son situaciones habituales y cada vez más frecuentes (ancianos) para la indicación de fármacos antihistamínicos. En esta revisión se exponen los datos más relevantes recopilados en cuanto al uso de antihistamínicos en estas situaciones especiales.

Palabras clave: Antihistamínicos H₁. Insuficiencia hepática. Insuficiencia renal. Niños. Ancianos. Embarazo. Embarazadas. Lactancia.

■ Abstract

Antihistamine drugs are one of the therapeutic classes most used at world level, at all ages and in multiple situations. Although in general they have a good safety profile, only the more recent drugs (second generation antihistamines) have been studied specifically with regard to the more important safety aspects. Given the variety of antihistamine drugs, they cannot all be considered equivalent in application to various special clinical situations, so that the documented clinical experience must be assessed in each case or, in the absence of such, the particular pharmacological characteristics of each molecule for the purpose of recommendation in these special situations.

In general, there are few clinical studies published for groups of patients with kidney or liver failure, with concomitant multiple pathologies (such as cardiac pathology), in extremes of age (paediatrics or geriatrics) and in natural stages such as pregnancy or lactation, but these are normal situations and it is more and more frequent (among the elderly) for antihistamine drugs to be recommended. This review sets out the more relevant details compiled on the use of antihistamines in these special situations.

Key words: Antihistamines H₁. Liver failure. Kidney failure. Children. The elderly. Pregnancy. Pregnant women. Lactation.

To comprehend fully the use of second generation antihistamines in situations such as kidney or liver failure or in the case of pharmacological interactions, it is necessary first to understand the metabolism and excretion of the various antihistamines. It must be borne in mind that drugs which are not metabolized, or only very little, have the advantage that there is a low risk of pharmacological interactions arising from the metabolism when they are administered concomitantly with other compounds. Also they present low inter-individual variability of pharmacokinetic parameters [1]. Comments are given below on the principal pharmacokinetic aspects of the most important second generation antihistamines in use today, specifically, bilastine, desloratadine, ebastine, fexofenadine, levocetirizine, mizolastine and rupatadine. On discussing desloratadine, an active metabolite of loratadine and levocetirizine and an active enantiomer of cetirizine, there is no specific discussion of cetirizine and desloratadine.

1. Bilastine

In experimental models it has been checked that bilastine does not go through intestinal or liver metabolism [2]. In a study of phase I carried out on healthy volunteers [3], it was observed that, after administration of a 20 mg dose of bilastine, approximately two thirds of the drug was recovered in the faeces and one third in the urine. In both cases, the drug was found practically without being metabolized.

2. Desloratadine

Desloratadine is intensely metabolized in the liver. Its principal active metabolite is 3-hydroxydesloratadine, although it shows less activity than desloratadine [4]. The enzyme responsible for this metabolism is not well known, although various enzymes of the cytochrome P450 (CYP450) system have been mentioned [1]. The elimination of desloratadine takes place as to 45% in the urine and 47% in the faeces [4].

3. Ebastine

Ebastine experiences a notable first pass effect after its oral administration, being practically totally metabolized to its active metabolite, carebastine [5]. The liver metabolism of ebastine is produced principally by CYP 450 enzymes, specifically CYP3A4, CYP2J and CYP4F [6]. 66% of the dose administered is excreted through the kidneys [7].

4. Fexofenadine

This compound is the principal metabolite of terfenadine. As such, fexofenadine suffers little liver metabolism, approximately 5% of the total oral dose [8]. Its excretion takes place 11% through the kidneys and about 80% by faeces [1].

5. Levocetirizine

Levocetirizine is metabolized very little, approximately 14% of the total dose. Following administration of ¹⁴C-levocetirizine to healthy volunteers, 85% of the drug marked is recovered in the urine and 13% in the faeces [9].

6. Mizolastine

Mizolastine undergoes intense metabolism in the liver, over 65% [10]. The principal change is glucuronidation through glucuronosyltransferases (UGT), although the isoenzyme CYP3A4 is also involved (and, to a lesser degree, CYP2A6 and CYP2D6) [11]. Its excretion takes place 84-95% by the faeces and 8-15% in the urine [10].

7. Rupatadine

Rupatadine goes through a notable pre-systemic metabolism when administered orally; the compound undergoes various processes of biotransformation oxidation, resulting in various metabolites, some of which maintain an antihistaminic activity. In studies carried out in vitro CYP3A4 has been identified as the principal isoenzyme involved in its transformation [12]. Bile excretion is its principal route for elimination. In a study in which 40 mg of [¹⁴C]-rupatadine was administered to healthy volunteers, 34.6% of the radioactivity was recovered in the urine and 60.9% in the faeces, with very little of the drug being recovered unmetabolized [13].

Use in renal insufficiency (Table 1)

1. Bilastine

The effect of renal insufficiency (RI) on the pharmacokinetics of bilastine has been assessed. In a study carried out with 24 adults (6 controls, 6 patients with mild RI, 6 with moderate RI and 6 with serious RI), it was observed that the plasma concentration of bilastine rose in the patients with RI. However, the increase in the area under the curve (AUC) was kept within the safety margins of the drug and no pattern of accumulation was observed after the administration of five repeated doses [14]. Nevertheless, given that bilastine is a substratum of P-glycoprotein (P-gp), the concomitant administration of drugs or foods capable of inhibiting P-gp should be avoided in patients with moderate or serious kidney problems, and in patients with kidney alterations who receive high doses of the drug [14].

2. Desloratadine

No studies are available which specifically assess the use of desloratadine in RI. In the case of loratadine, a study has been done with healthy volunteers, on patients with RI with creatinine clearance over 30 ml/min and in patients on dialysis [15]. No significant differences were

Table 1. Routes of excretion of the principal second generation antihistamines and their use in kidney failure (RI)

Drug	Faecal excretion	Renal excretion	Comments
Bilastine	67%	33%	Not necessary. Avoid the concomitant administration of bilastine and P-gp inhibitors in patients with moderate or serious kidney failure.
Desloratadine	47%	45%	Use with precaution in serious kidney failure
Ebastine		66%	No need to adjust the dose
Fexofenadine	80%	11%	No need to adjust the dose
Levocetirizine	13%	85%	Adjust the dose according to the creatinine clearance function. Contraindicated if <10 ml/min
Mizolastine	84-95%	8-15%	Not specified
Rupatadine	61%	35%	Not recommended through lack of experience

observed in the $t_{1/2}$ of loratadine or in the C_{max} or T_{max} of descarboethoxyloratadine.

3. Ebastine

Mild to serious RI does not produce any clinically significant alteration in the pharmacokinetics of carebastine, in spite of the fact that the studies show a change in the $t_{1/2}$ [16]. It is not necessary to change the dose in patients with RI [7].

4. Fexofenadine

The pharmacokinetics of a single dose of 80 mg fexofenadine has been evaluated in 29 patients with various degrees of RI. In patients on dialysis an increase in the AUC, C_{max} and $t_{1/2}$ was observed, with respect to healthy subjects [17].

5. Levocetirizine

There are no studies available on the use of levocetirizine in RI. However, there are studies on cetirizine. Thus, in a study carried out on 30 healthy subjects of various ages and 15 patients with various degrees of RI, an increase was observed in the cetirizine elimination half life and reduced kidney clearance in patients with RI [18]. For their part, Noiri et al [19], in a study of the administration of multiple doses of cetirizine in patients on hemodialysis, concluded that the dose of 5 mg three times a week was an adequate and safe dose in this type of patient. In the case of levocetirizine, the technical file recommends adjusting the dosage intervals in

the case of RI. It is considered contraindicated in patients presenting terminal RI [20].

6. Mizolastine

In patients with chronic RI, it is observed that the $t_{1/2}$ is prolonged by 47% with respect to healthy young volunteers [11]; however, the levels remain within the range of values seen in healthy young adults and there seems to be no need to adjust the dose in chronic RI [10].

7. Rupatadine

No studies are available on rupatadine in patients with RI. At present its use is not recommended in this type of patients [21].

Use in liver failure (Table 2)

The use of any antihistamine can precipitate liver encephalopathy, in cases of serious liver failure.

1. Bilastine

Taking into account that bilastine is not metabolized and that kidney clearance is its principal route of elimination, liver failure is not expected to increase the systemic exposure above the safety margin. For this reason it is not necessary to adjust the dose in patients with hepatic insufficiency (HI) [22].

Table 2. Liver metabolism of the principal second generation antihistamines and possible interactions through this mechanism

Drug	Liver metabolism	Pharmacological interactions	Adjustment of dose in HI
Bilastine	No	No	Not necessary
Desloratadine	Very extensive to 3-hydroxydesloratadine	Improbable	Not necessary
Ebastine	Yes, carebastine CYP3A4, CYP2J and CYP4F	Yes	Not necessary in mild and moderate HI In serious HI do not administer more than 10 mg
Fexofenadine	5%	No	Not necessary
Levocetirizine	14 %	Improbable	Not necessary
Mizolastine	More than 65% Principally UGT, CYP3A4	Yes	Contraindicated in serious HI
Rupatadine	Extensive liver metabolism (desloratadine) CYP3A4, biliary elimination	Yes	Not recommended through lack of experience

Abbreviation: UGT: glucuronosyltransferases. HI: Hepatic insufficiency. CYP: cytochrome P.

2. Desloratadine

In a study carried out with patients with minor, moderate and serious HI (four per group), the degree of exposure to a single dose of desloratadine was not varied in relation to liver dysfunction. As a whole, the C_{max} and AUC were higher in patients with liver dysfunction with respect to the controls, although the exposure did not exceed that of a high dose of desloratadine (45 mg/day for 10 days) and no adverse effects were observed [4]. It is thought that the therapeutic dose of 5 mg is safe in patients with HI.

3. Ebastine

HI does not modify the pharmacokinetic parameters of carebastine in a clinically significant way [23]. It must be said that in patients with serious HI only a 10 mg dose has been assessed and no drugs affecting liver function have been used concomitantly, so that both circumstances must be borne in mind in clinical practice when prescribing this preparation.

4. Fexofenadine

The pharmacokinetics of fexofenadine in HI has been assessed in a group of 10 patients with mild to moderate HI and in a group of 7 patients with moderate to serious HI [24]. After the administration of a single oral dose of 80 mg fexofenadine, the pharmacokinetic profile of these patients was similar to that of healthy subjects and the drug was well tolerated. These findings suggest that it is not necessary to adjust the dose for patients with HI [24].

5. Levocetirizine

In not being metabolized by the liver, there is no need to adjust the dose in patients suffering only from liver failure [25].

6. Mizolastine

In patients with cirrhosis given mizolastine, there is an increase in T_{max} , a reduction of C_{max} , an increase in the average distribution life and an AUC 50% higher than in healthy volunteers [11]. In the technical file the drug is considered contraindicated in the case of significant alterations in liver function [26].

7. Rupatadine

There is no experience in patients with HI, so that at present its use is not recommended in this type of patients [21].

Second generation antihistamines and pharmacological interactions

Pharmacological interactions have the potential of being an important cause of morbidity in treatments with medication. This could be the result of an interference in the absorption process, through the active transport mechanisms (for example P-gp or organic anion-transporting systems –

OATP-), or could also be due to the inhibition or induction of liver metabolism through the cytochrome P450 system [27]. When the interactions produce a reduction in the plasma concentrations of the drug the result can be a reduction in effectiveness, while if the result is an increase in the plasma levels of the drug, the result could be the appearance of side effects. The best known example is the case of astemizole and terfenadine and the risk of the appearance of torsade de pointes arrhythmia when administered jointly with erythromycin or ketoconazole [28].

Current European Directives (Directive CPMP/EWP/560/95, updated in 2010) require, for all new drugs in development, investigation of the cytochrome P450 metabolic route. In this sense, one of the drugs most used is ketoconazole, which inhibits the cytochrome P450 3A4 system; it should be remembered that, at the same time, it inhibits the P-gp.

The cytochrome P450 system is constituted by microsomal enzymes belonging to the hemoprotein family and found in the enterocytes and hepatocytes. There are 14 families and 17 subfamilies and, in the case of H₁ antihistamines, the most important metabolic enzymes are CYP2D6 and CYP3A4 [29].

For its part, P-gp is a natural detoxification system which is localised in normal tissues which have secretory or barrier functions. Thus, it is localised in the small and large intestines, in bile canaliculi, proximal kidney tubules, vascular endothelial cells of the CNS, the placenta, adrenal glands and testicles [30]. The P-gp behaves as an extraction pump saturable at high concentrations of substratum. If a certain drug is a substratum of P-gp, its absorption will be reduced in the intestinal ambit (on being expelled into the lumen of the digestive tubes), but will have difficulties in crossing the hematoencephalic barrier.

Finally, the organic anion-transporter polypeptides (OATP) are membrane transporters which introduce substances into the interior of the cell and regulate the cellular collection of a series of endogenous compounds and drugs [31]. The OATP human family consists of 11 members: OATP1A2, 1B1, 1B3, 1C1, 2A1, 2B1, 3A1, 4A1, 4C1, 5A1 and 6A1.

Grapefruit juice has two actions; on the one hand, the furanocoumarins which it contains interfere with the CYP 450 enzymatic system, in an effect which lasts for around 24 hours; on the other hand, flavonoids are P-gp activators and interact with the OATP, in an effect which can last for around 3 hours [32].

1. Bilastine

The administration of 20 mg bilastine together with 400 mg ketoconazole for six days caused an increase in the systemic concentration (in steady state) to double, without changes in the clearance of the drug, which suggests that the effect is due to inhibition mediated by the P-gp system and not on liver metabolism [33].

2. Desloratadine

The joint administration of 7.5 mg desloratadine with ketoconazole was assessed, observing an increase of 1.45 times in the C_{max} and 1.39 in the AUC of desloratadine. Something similar happened with the concomitant administration of erythromycin, with the two parameters being increased by 1.2 and 1.1 times, respectively. No adverse cardiac or sedative effects were produced, so that desloratadine seems safe when administered with drugs inhibiting CYP450 [4].

3. Ebastine

As ebastine is metabolized by the CYP450 system, it can produce interactions with drugs which affect this system. Thus, the administration of 20 mg daily of ebastine with 400 mg of ketoconazole for 10 days produced an increase in the AUC, C_{max} and t_{max} of carebastine and ebastine, although there was no increase of QTc [34].

4. Fexofenadine

The concomitant administration of fexofenadine with ketoconazole or erythromycin produces an increase in the AUC of 2.6 and 2 times, respectively. However, these levels are within those catalogued as safe in clinical studies [8]. This increase has been attributed to an increase in gastrointestinal transport due to the effect of these drugs.

5. Levocetirizine

No data are available on levocetirizine. However, the administration of ketoconazole or erythromycin does not produce alterations in the pharmacokinetics of cetirizine [1].

6. Mizolastine

The administration of mizolastine with 400 mg of ketoconazole produces a doubling in the AUC of the former, but without changes in the half life of elimination [10]. In a study lasting 16 days, with administration of 10 mg mizolastine with 1g erythromycin twice a day there was an increase in the levels of mizolastine and a 50% increase in the AUC from day 11 to day 16 [10].

7. Rupatadine

The pharmacological interactions of rupatadine (20 mg) with ketoconazole (200 mg) and erythromycin (500 mg) were evaluated [35]. Both compounds produced an inhibition of the pre-systemic and systemic metabolism of rupatadine, resulting in an increase of 10 and 2-3 times, respectively, in the levels of unaltered drug. In spite of this increase in the plasma concentrations of the drug, no clinically significant changes were produced, including the QTc interval. Nevertheless, due to these potential interactions, the use of rupatadine in combination with CYP 450 inhibitors is not recommended [13].

Table 3. Recommendations in the technical file on the principal second generation antihistamines in relation to patients with cardiology problems

Drug	Recommendation (TF)
Bilastine	None in particular
Desloratadine	None in particular
Ebastine	Administer with precaution in patients with known cardiac risks, such as patients with prolonged QT interval, hypokalemia, concomitant treatment with drugs which increase the QT interval or which inhibit the enzyme CYP3A4
Fexofenadine	None in particular
Levocetirizine	None in particular
Mizolastina	Contraindicated for concomitant administration with macrolide antibiotics or systemic imidazole antifungal medication Contraindicated when there is clinically significant cardiac illness or a background of symptomatic arrhythmias Contraindicated in patients with known or suspected prolongation of the QT interval or electrolytic imbalance, in particular clinically significant hypokalemia, bradycardia or with drugs which prolong the QT interval
Rupatadine	Must be used with precaution in patients with prolongation of the QT interval, hypokalemie, and in patients with pro-arrhythmic conditions such as clinically significant bradycardia or acute myocardiac ischemia

Abbreviations: TF: technical file. CYP: cytochrome P.

Cardiac effects of antihistamines (Table 3)

At the end of the last century, cases began to be described of torsade de pointes (arrhythmia susceptible of leading to episodes of ventricular tachycardia, ventricular fibrillation or death), in relation with the administration of terfenadine or astemizole, two of the initial second generation antihistamines. In most of these cases this was due to an overdose, absolute [36] or relative, generally the result of an interaction with drugs which inhibited the cytochrome P450 system [37, 38]. This led, in the majority of countries, to the withdrawal of terfenadine and astemizole from the market.

The mechanism responsible for these cardiac effects is the capacity of both antihistamines to interfere in one of the potassium currents involved in cardiac repolarization, IKR, and produce a prolongation of the QT interval.

Congenital syndromes of long QT have been associated with the hERG gene (*human ether-a-gogo related gene*), which codifies the alpha subunit of the channel responsible for the potassium current referred to above. The channel is formed by four subunits which are arranged forming a pore [39], which is where the drug can interact and produce the blockage.

The arrhythmias which occurred with astemizole and terfenadine led to the supposition that it would be a class effect of antihistamines; however it has been amply demonstrated that this is not so [40]. Nevertheless,

it has led the regulating authorities to demand a series of studies in vitro and in vivo, in animal and human models, to assess the effect of antihistamines on cardiac repolarization [41].

1. Bilastine

The capacity of blocking the hERG channel (CI50), determined in cultures of HEK-293 cells, was established in 6.5 μM [2]. In the case of terfenadine or astemizole, the CI50 is of the nanomolar order [42]. A study was carried out on 30 healthy volunteers, following the regulation ICH (*International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*) E14, with the administration, once a day for 4 consecutive days, of 20 mg bilastine, 100 mg bilastine, 20 mg bilastine plus 400 mg ketoconazole, placebo and 400 mg moxifloxacin as positive control [43]. In the study it was found that bilastine, in monotherapy, at therapeutic and suprathreshold doses, had no effect on the MCS (*Morphology Combination Score*), which evaluates the morphology of the T waves, or on the QTcF (QTc with the Fredericia correction). An increase was observed in the QTcF when bilastine and ketoconazole were administered together, although the authors concluded that this effect was due almost exclusively to the effect on repolarization of the ketoconazole and not the bilastine.

2. Desloratadine

Studies carried out on oocytes of *Xenopus laevis* showed no effect of desloratadine on the hERG channel function [44]. Nor was any effect observed in studies carried out in vivo on various animals. In a study carried out in humans, with 45 mg desloratadine administered for 10 days, no effect on the ECG was observed, in particular on the QTc [45]. The administration to healthy volunteers of 7.5 mg desloratadine together with ketoconazole or erythromycin showed no alteration of the ECG parameters [46, 47].

3. Ebastine

The administration of ebastine alone, at the recommended doses of 10 and 20 mg had no effect on the QT interval [48]. In a randomized study, 60 mg ebastine, 100 mg ebastine, 180 mg terfenadine and placebo were administered for 10 days to 32 healthy volunteers [49]. When the QT interval was analysed with Bazett's correction, it was observed that the result obtained with the 60 mg dose of ebastine was not significantly different from that obtained with placebo. However, there were significant differences with the 100 mg dose of ebastine and the 180 mg of terfenadine. In the case of ebastine, these differences with respect to the placebo group disappeared on using the Fredericia correction, although this did not happen in the case of terfenadine. In another study evaluating the dose of bilastine, a single dose of 80, 150, 300 and 500 mg was administered to 6 healthy volunteers [50]. No change greater than 10% was observed in the QTc (with various formulas) or any QTc value above 500 ms.

The concomitant administration of 20 mg ebastine with 400 mg ketoconazole produced a significant increase in the QTc interval of 12 ms, although it was not significantly different from that observed with ketoconazole (7 ms) [33]. These changes seem to be similar to those produced by the concomitant administration of cetirizine or loratadine and ketoconazole [48]. The administration of 20 mg ebastine to patients who received multiple doses of 2000 mg erythromycin stearate did not produce significant changes in the QT, although it did with the addition of 20 mg ebastine to 2400 mg of erythromycin ethylsuccinate [48].

The technical file on the product recommends its administration with precaution in patients of known cardiac risk, such as patients with prolongation of the QT interval, hypokalemia, concomitant treatment with drugs which increase the QT interval or which inhibit the CYP3A4 enzyme [51].

4. Fexofenadine

Fexofenadine, in doses of up to 800 mg once a day or 690 mg twice a day does not produce an increase in the QT interval. In long-term studies carried out on patients who received 80 mg twice a day for 3 months, 60 mg twice a day for two months or 240 mg once a day for 12

months, no significant alterations were observed in the QT interval [52].

The administration of 120 mg fexofenadine with 400 mg ketoconazole once a day or 500 mg erythromycin three times a day to healthy adults did not produce significant increases in the QTc [53].

5. Levocetirizine

In a double blind study carried out with 52 healthy subjects who were given 5 mg levocetirizine, 30 mg levocetirizine, placebo or moxifloxacin, no alterations were observed in the QT interval [54].

6. Mizolastine

At the dose normally used in clinical practice, mizolastine does not produce alterations in cardiac repolarization [55]. In a double blind study, randomized and controlled with placebo, carried out on 24 healthy volunteers, in which they were given 10, 20 and 40 mg mizolastine against placebo, no alterations were observed in the QT interval or in cardiac repolarization [56].

In studies in vitro, carried out with oocytes of *Xenopus* frogs, it was observed that mizolastine has a certain capacity to inhibit the hERG channel, at concentrations above those reached after a therapeutic dose, which could have some clinical significance in patients with a risk of developing arrhythmias [57].

7. Rupatadine

In a study carried out on 160 healthy volunteers following the ICH E14 recommendations, they were given 10 mg rupatadine, 100 mg rupatadine for 5 days, against placebo, with 400 mg moxifloxacin as positive control, although in this case without a ketoconazole arm, and no alterations were observed in cardiac repolarization [58].

Use of antihistamines during pregnancy

Pregnancy constitutes a physiological period in a woman's life which is often treated excessively from a medical viewpoint. It has been observed that pregnant women consume an average of eleven different medicines during the nine months before the birth and seven during labour and delivery [59]. Antihistamines are one of the therapeutic groups most used during pregnancy [60] together with analgesics, antacids and antiemetics.

Any medicine used during pregnancy can be potentially harmful to the foetus. However, of the 2-4% of newborn babes with congenital anomalies, only 1% of these foetal malformations can be attributed to the consumption of medication, although it is considered that many of them would be avoidable.

In pregnant women the action of medicines on the foetus

Table 4. Classification by the U.S. Food and Drug Administration (FDA) for the administration of medicines during pregnancy

Category	Studies in animals	Human data	The benefit can exceed the risk
A	Negative ¹	Negative studies ²	Yes
B	Negative	Studies not made	Yes
B	Positive ³	Negative studies	Yes
C	Positive	Studies not made	Yes
C	Not made	Studies not made	Yes
D	Positive or negative	Studies or reports +	Yes
X ⁴	Positive	Studies or reports +	No

Abbreviation: +: positive

¹With no demonstrated teratogenicity

²Adequate controlled studies in pregnant women

³Teratogenicity demonstrated

⁴Contraindicated in pregnancy

depends on the dose, the route of absorption, the duration of exposure and the specific moment of exposure, the period of embryogenesis (from 4 to 10 weeks of gestation) being the most susceptible, although the possible effects of medication during the rest of the period cannot be underestimated (for example, abnormalities of teeth and bones due to tetracyclines, congenital hearing loss due to aminoglycosides, the effect of corticoids on foetal growth or the unknown long-term effects on the development of the central nervous system of many medicines administered to pregnant women).

The USA Food and Drug Administration, (FDA) has established a series of categories in order to determine the potential of medicaments to cause adverse effects during pregnancy, obliging the manufacturers of medicines to classify them in one of these categories (Table 4).

From a general viewpoint, antihistamines as a therapeutic class have demonstrated being sufficiently safe for administration during pregnancy. Various studies of an epidemiological type have not found any association between taking antihistamines during pregnancy and the appearance of greater or lesser birth defects: Studies of cases-controls such as that of Nelson in 1971, with 458 newborns with birth defects, that of Anderson's cohorts in 1991, with 5,401 women exposed to antihistamines, the prospective study by Schatz in 1997, with the monitoring of 493 women exposed to antihistamines or the meta-analysis by Seto in 1997, which included studies which grouped together more than 200,000 women exposed to antihistamines during the first three months, did not find any higher risks in these women than in those who did not take antihistamines [61].

In an exhaustive statistical analysis carried out on the continuous epidemiological survey made in the U.S. entitled "*National Birth Defects Prevention Study*" it was concluded that, in general, the results were fairly convincing with regard to the absence of a relation between the use of antihistamines

during pregnancy and birth defects, however, a series of statistically significant associations were detected which should be taken into account: Harelip is weakly associated with the taking of any antihistamine during pregnancy; thus, diphenhydramine was associated with eight different types of birth defects although only weakly; the risk of spina bifida was associated with four antihistamines (diphenhydramine, doxylamine, pheniramine and promethazine) as well as with the taking of any antihistamine (although the relation was weak): meclizine was associated imprecisely but importantly with the appearance of cleft palate, while promethazine and doxylamine were weakly associated with heart defects. Only in the case of loratadine was a positive association found between a non-sedative antihistamine (second generation) and birth defects. The authors concluded that, given that the data were retrospective and self-assessed, the high number of associations detected should be investigated more exhaustively [62].

There are few specific epidemiological studies with regard to the teratogenicity of sedative antihistamines (first generation): Heinonen in 1977 reported a large-scale prospective study to investigate the teratogenicity of many medicaments which detected an association of the administration of chlorpheniramine and meclizine with sight and hearing defects. However, the rest of the analyses in this study did not detect any association between specific antihistamines and birth defects. Ferencz in 1993, in a retrospective study of cases-controls, found no association of cardiac birth defects when the pregnant women took antihistamines three months before the pregnancy and during the first three months [62].

The review by Schatz in 2002 reported studies in humans in which a relation was detected between the use of first generation antihistamines and the appearance of birth defects: brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, hydroxyzine,

pheniramine and triprolidine, have communicated relative risks greater than 1, although many of these antihistamines were not teratogenic in animal studies [61].

Second generation or non-sedative antihistamines have been studied much more exhaustively than those of the first generation and their safety data are much more sound, so that at present these are recommended for normal use. However, data for pregnant women are difficult to obtain, as this is a group protected from carrying out clinical trials.

Data obtained from studies in animals have determined that antihistamines such as astemizole, terfenadine or fexofenadine and azelastine, levocabastine and olopatadine (for external use), are class C according to the FDA regulations, due to their teratogenicity in animals. Cetirizine, loratadine, ebastine, levocetirizine, desloratadine, rupatadine and bilastine have demonstrated an absence of teratogenicity in studies on animals. From the data available on studies in humans it is understood that cetirizine [63] and loratadine [64] are the best studied, with sufficient data available for cohorts of pregnant women to be included in category A of the FDA, although they are still in category B.

There are no studies in pregnant women which offer controlled data on the risk of teratogenicity for ebastine, levocetirizine, desloratadine, rupatadine or bilastine. Levocetirizine belongs to class B according to the FDA, desloratadine to class C, as neither rupatadine nor bilastine are marketed in America they have not been assigned to any class by the FDA.

Allergic rhinitis and urticaria are not life threatening illnesses but their effect on patients suffering from them can be significant. The symptoms of these illnesses occur frequently during pregnancy and require treatment to alleviate them, which must be selected taking very much into account the risk-benefit ratio for both the mother and the foetus. Table 5 shows the classification that the FDA has given to the majority of the antihistamines available in the market and allows an assessment of these in terms

Table 5. Categorizing by the U.S. Food and Drug Administration (FDA) for the principal first and second generation antihistamines

Antihistamine	FDA Class
<i>First Generation</i>	
Chlorpheniramine	B
Dexchlorpheniramine	B
Promethazine	C
Hydroxyzine	C
Tripeleminamine	B
<i>Second Generation</i>	
Cetirizine	B
Loratadine	B
Fexofenadine	C
Desloratadine	C
Levocetirizine	B

of risk against expected benefit. Most of the classic consensus documents recommend the use of first generation antihistamines to minimise the risk in pregnancy, due to a longer time of pharmacovigilance without any worrying data. However, from the data collected in this review, it is possible to deduce that first generation antihistamines have a potential risk, although low, of teratogenicity during the first three months and also are less safe in terms of adverse effects than those of the second generation. There are sufficient data available for safety in pregnancy for some of the second generation antihistamines (cetirizine and loratadine) so that they can safely be recommended during pregnancy.

Use of antihistamines in breast-feeding

From a pharmacokinetic viewpoint almost all drugs pass into the maternal milk, generally by mechanisms of passive diffusion, although, in average terms, this means less than 2% of the dose administered to the mother. It must be borne in mind that the transport of drugs to the maternal milk is greater when the union to plasma proteins in the mother is low or when the liposolubility of the drug is high. Basic drugs reach the maternal milk more easily and ionization favours this passing of drugs. It must also be taken into account that at the end of the feed, the milk contains more fat and that this favours the passing of lipophilic drugs.

In a prospective monitoring by a telephone survey of mothers in the breast-feeding period who were taking some medication it was deduced that, in general, the use of antihistamines in these mothers is not related with serious adverse effects on the breast-fed baby, and only some cases of dryness or irritability were reported when the mother was taking first generation antihistamines [65]. There were also some cases reported of irritability in breast-fed babies of mothers who were taking astemizole or terfenadine, although in no case was it reported that medical treatment was needed [61].

In studies with loratadine/desloratadine [66] and terfenadine/fexofenadine [67] percentages of detection in maternal milk of 1.1% and 0.45%, respectively, were established, which allows an assurance of minimal exposure of the breast-fed baby in mothers who require these treatments. This minimal risk determines that these are the antihistamines of choice for breast-feeding mothers.

Use of antihistamines in children

Medicines with antihistamine action are one of the therapeutic groups most used in paediatrics. According to data obtained by the allergy study in 2005 by the Sociedad Española de Alergología e Inmunología Clínica (*Spanish allergology and clinical immunology society*), 56.4% of the paediatric patients (under 14 years) of the study had

Table 6. Noted pharmacokinetic aspects of antihistamines in the paediatric age

Drug	Dose studied (mg or mg/kg*)	Patients (N)	Age (years)	Cp max (ng/mL)	t max (hours)	t _{1/2} (hours)	↓ erythema/hives (hours)
1st Generation							
Brompheniramine	4	14	9.5±0.4	7.7±0.7	3.2 ±0.3	12.4 ± 1.1	0.5 a 36
Clorpheniramine	0.12*	11	11 ± 3	13.5 ± 3.5	2.5 ± 1.5	13.1 ± 6.3	1 a 24
Diphenhydramine	1.25*	7	8.9±1.7	81.8±30.2	1.3 ± 0.5	5.4 ± 1.8	1 a 12
Hydroxyzine	0.7*	12	6.1±4.6	47.4±17.3	2.0 ± 0.9	7.1 ± 2.3	n/d
Ketotifen	1 (c/12h)	6	3 ± 1	3.25	1.33	n/d	n/d
2nd Generation							
Cetirizine	5	10	8±0.6	427.6±144.2	1.4 ± 1.1	7.1 ± 1.6	1 a 24
	10	9	8±0.6	978.4±340.6	0.8 ± 0.4	6.9 ± 1.6	0.5 a 24
	5	8	2.7	560±200	1.44 ± 1.1	4.9 ± 0.6	n/d
	0'25	15	12.3±0.46	390±135	2 ± 1,3	3.1 ± 1.8	90% a las 12 horas
Ebastine	5	10	7.3±0.4	108.6±11.8	2.8 ± 0.3	11,4 ± 0,7	0.5 a 28
	10	10	7.8±0.4	209.6±24.2	3.4 ± 0.4	10.1 ± 1.1	0.5 a 28
Fexofenadine	30 (c/12 h)	14	9.8±1.8	178 ± 22	2.4 ± 0.2	18.3 ± 1.2	1 a 24
	60 (c/12 h)	14	9.8±1.8	286 ± 34	2.4 ± 0.2	17.6 ± 1	1 a 24
	30 (c/12 h)	50	2-5	224			
Loratadine		10	13	10.6	4,38	1	13.79 1 a 12
	5	18	3.8±1.1	7.8	1,2	n/d	n/d
Levocetirizine	0.125* (c/12h)	15	20.7±0.31	286 ± 68	1	4.1 ± 0.67	1 a 28
	0.18*	14	8.6±0.4	450 ± 37	1.2 ± 0.2	5.7 ± 0.2	n/d
Desloratadine	1	58	>0.5 ≤1				
	1,25		1-2				

Abbreviations: Cp max: Maximum plasma concentration. t max: Time to reach maximum plasma concentration. t_{1/2}: Half life

taken some antihistamine drug before visiting the allergist, 22% of these being first generation antihistamines. In Spain, according to data from the IMS, in 2006 around two million units of antihistamines were sold for paediatric use (in solution), which meant spending of nearly 6 million euro. Of this total, 34% were first generation or sedative antihistamines.

The correct use of medicines for children means accepting a large quantity of differential aspects with respect to the use for adults, thus leading to the existence of a differentiated discipline, paediatric clinical pharmacology, which seeks to forecast the organism's response to drugs at the paediatric age, from the viewpoint both of their therapeutic effectiveness and of their adverse effects, through studies based on pharmacokinetics and pharmacodynamics.

From the pharmacological viewpoint the child is not an adult in miniature, but an organism in a constant process of maturing and development, which leads to the definition of several subgroups in the paediatric stage, each

with its own peculiarities: premature babies, the newborn, breast-fed babies, infants, children and adolescents, with the pharmacokinetic and pharmacodynamic particularities typical of each group [68].

From the pharmacokinetic viewpoint there are many differential aspects to be taken into account: the absorption processes (greater in the new born for example), distribution (greater distribution volume, greater fraction of free drug at lower ages), the immaturity of most of the metabolic reactions in metabolism, the immaturity of excretion processes (increase in the average life of the drugs). There are also pharmacodynamic differences such as irregularity in the presence of number and functional nature of receptors for the various drugs, the effects on growth, maturity, intellectual development and the psyche [68].

All these aspects determine the need for specific pharmacological studies in paediatric ages, as is already set out in their regulations by the various European and US medicine agencies, to understand the pharmacology at these ages in detail and be able to establish adequate

galenic formulations, doses and dosage intervals for each paediatric age.

The pharmacokinetics and pharmacodynamics of medicines can differ a great deal depending on the age group with which the study is made. These characteristics determine aspects of effectiveness and above all safety and allow a forecast to be made of the behaviour of the medicine in the organism. Table 6 shows the most important pharmacological aspects, according to published studies on the antihistamines most used in paediatrics.

In general, antihistamines are medicines with good absorption following oral administration, in both liquid and solid formulations, reaching their maximum plasma concentrations between 1 and 4 hours in paediatric ages, the same as for adults. The plasma half life depends on the processes of metabolism and clearance of the drug in the organism. These processes are the same for paediatric and adult ages, but in the revised studies a more rapid metabolism or elimination is found for some of the antihistamines, with the result that the ideal dosage is every twelve hours instead of every 24 hours, as happens for levocetirizine in pre-school children.

All the first generation antihistamines, and most of the second, are metabolized in the liver through the cytochrome P450 systems. Only cetirizine, levocetirizine, fexofenadine and bilastine are eliminated in a high percentage without metabolizing, in urine for the first two and fundamentally by the digestive route for the last two.

There are no studies which document the effects in paediatric ages of possible medication interactions between antihistamines and cytochrome P450 inhibitor drugs or which are metabolized through it, except a study of children with malaria resistant to treatment with chloroquine, in which it was found that the plasma concentrations of this drug were significantly greater and were reached earlier when it was administered jointly with chlorpheniramine.

The pharmacodynamic aspects, such as the start and the duration of action, were studied in paediatrics in the same way as for adults, using the model of the inhibition of hives and cutaneous erythema induced by histamine. The last column of Table 6 shows the interval of time in which a significant inhibition of hives and erythema is produced by the various antihistamines, checking that the action starts for most of them in the first hour, and lasts up to the first 24 hours. The same as for adults, the absence was checked of tachyphylaxis or tolerance for this effect on hives and erythema induced by histamine [69].

The medicines agencies of the various countries and the international agencies recognise that at present there are many medicines marketed and authorised for their use in children which have never been adequately investigated for these age groups, but which were given authorisation at the time through lack of regulation of the requirements demanded, and their use has been maintained due to the pharmacovigilance systems not having detected any alert as to adverse effects which

would mean their removal from the market. Many of the recommendations for antihistamines in children have been made by extrapolation of their effects on adults, and what is worse, the calculation of the paediatric dosage has been done with little or no detailed knowledge of pharmacokinetics in the different paediatric age groups.

At present, these medicine agencies require that, for any new medicine for which authorization is requested for use in paediatric ages, specific studies must be produced on safety in the paediatric ages for which the authorization is requested.

First generation antihistamines have been little studied from the viewpoint of safety in children. Diphenhydramine and hydroxyzine were assessed, from the objective viewpoint of their affecting the cognitive processes, latency of P300 potential, and the somnolence that they produce, through the use of an analogue visual scale, in children with allergic rhinitis. In these studies both drugs caused objectivable dysfunction of the central nervous system (CNS) and somnolence. Also the action of chlorpheniramine, terfenadine and placebo on the CNS was assessed in a group of children with allergic rhinitis, with the conclusion that neither terfenadine nor the placebo produced changes in cognitive affectation, while chlorpheniramine did. In another study carried out with 24 children aged from 7 to 14 diagnosed with allergic rhinitis, it was shown that both chlorpheniramine and cetirizine produced a significant cognitive alteration as against the placebo, but this affectation was not correlated with changes in the subjective appreciation of this affectation using an analogue visual scale [69].

As well as the effects on the CNS, first generation antihistamines, due to their action on other receptors distinct from the histamine receptor, can cause adverse effects such as alterations of vision, dryness in mucous membranes and other effects arising from their anticholinergic action. Through their action on serotonergic receptors some antihistamines can cause increased appetite and weight gain. This effect has been known for a long time for cyproheptadine (published in 1962) and it is currently used as a therapeutic indication [70]. Multiple rare adverse effects have been communicated in children who were taking first generation antihistamines, such as spasms, convulsions, aggressiveness, respiratory distress, fixed exanthema, central anticholinergic syndrome and toxic encephalopathy in patients with cutaneous syndromes (atopic dermatitis, chickenpox) with damage in the cutaneous barrier, to which external first generation antihistamines were applied [71].

Second generation or non-sedative antihistamines were developed through the need to avoid the adverse effects on the CNS of the first generation antihistamines. From the viewpoint of clinical pharmacology, the second generation antihistamines have been much better documented than the classical ones, with the availability of many clinical studies with data on safety in different age groups, for those antihistamines which have registered indications in paediatric ages: cetirizine [72, 73], levocetirizine [74], loratadine [75], desloratadine [76], ebastine [77] and fexofenadine [78, 79]

have been well documented for their safety in the short, medium and some in the long term.

One of the principal adverse effects documented for second generation antihistamines, which led to the removal from the market (in many countries) of antihistamines such as terfenadine or astemizole, is the appearance of cardiac arrhythmias. In children treated with astemizole cases have been reported of syncope during or after physical exercise, loss of consciousness or palpitations. The absence of cardiotoxicity in antihistamines such as cetirizine, loratadine, fexofenadine and ebastine is well documented in children and adults [69].

It can be concluded that second generation antihistamines with approved indications for their use in paediatric ages

have their safety and effectiveness much better documented than first generation antihistamines, so that in general, the habitual use of the latter is not justified, except when some of their side effects become desired effects (increased appetite, sedation, dryness of mucous membranes).

Use of antihistamines in the elderly

The increased life expectancy in the world population has meant that the number of senior citizens has grown substantially in recent decades. Allergic illnesses have increased in occurrence in all age groups and particularly in

Table 7. Aspects to take into account in the use of antihistamines in the elderly

Drug	Important pharmacokinetic characteristics		Specific adverse effects	Contraindications	Drug interactions
	Metabolism	Elimination			
Cetirizine	<40% through liver Dose adjustment in HI	Kidney route Dose adjustment in RI	Headache, vertigo, agitation, somnolence, urine retention	Serious RI	Sedatives Theophyllines
Loratadine	High % through liver. Half life increases with age Dose adjustment in HI	Kidney route Dose adjustment in RI	Alopecia, liver dysfunction, cutaneous allergic reactions	Medication which inhibits liver metabolism of loratadine	Ketoconazole, erythromycin, cimetidine
Ebastine	High % through liver Dose adjustment in HI	Kidney route Dose adjustment in RI	Headache, xerostomia, pharyngitis, asthenia, flu syndrome, somnolence	Serious HI or RI	Ketoconazole Erythromycin
Fexofenadine	<8% through liver No dose adjustment required in HI	Bile /12% kidney route Dose adjustment in RI	Headache, somnolence, vertigo, nausea	None	Erythromycin, ketoconazole, antacids containing aluminium or magnesium
Levocetirizine	<15% through liver Dose adjustment in HI	Kidney route Dose adjustment in RI	Headache, somnolence, xerostomia, rhinorrhea nose, pharyngitis, stomach ache, migraine	Intolerance to lactose, galactosemia, poor absorption of galactose/glucose	None
Desloratadine	High % through liver Dose adjustment in HI	Kidney route Dose adjustment in RI	Sedation, xerostomia and headache	Serious RI	None
Rupatadine	High % through liver Dose adjustment in HI	Bile/kidney route Dose adjustment in RI	Somnolence, headache, fatigue, asthenia, dry mouth and dizziness	Precaution in patients with prolongation of the QT interval, hypokalemia and cardiac pathology Precaution in the elderly	Ketoconazole Erythromycin Grapefruit juice Alcohol Sedatives
Bilastine	No liver metabolism No dose adjustment required in the elderly	Bile/kidney route No dose adjustment required in RI	Headache, somnolence, dizziness and fatigue	None	Ketoconazole Erythromycin Diltiazem Grapefruit juice Cyclosporine Ritonavir Rifampicin

Abbreviations: HI: Hepatic insufficiency. RI: Renal insufficiency.

the elderly [80], which means that there is a need to study the special characteristics of the use of anti-allergic medication in these ages.

According to data from the World Health Organization (WHO) between 65 and 90% of the elderly consume some medicines and a very high percentage of them are multi-medicated. It has been found that the frequency of adverse reactions to medicines increases considerably with age, being at a maximum in adults of over 80 years.

Various factors determine the response to drugs at advanced ages. Some factors can be considered as non pharmacological, such as the coexistence of multiple illnesses, the atypical presentation of them, failure in compliance (due to cognitive alterations, cultural and economic factors), with the multi-medication. However, the pharmacological factors must be well taken into account as they can be generally understood and are related with the differential characteristics of pharmacokinetics and pharmacodynamics in this age group, which can be summarised as:

- Alterations in the absorption of medicines, although it seems that this is one of the less affected pharmacological parameters: through lower gastric acidity, reduction of the absorption surface, reduced intestinal mobility or delay in gastric evacuation.
- Alterations in the distribution of the drugs, due to the different organic composition: reduction in body water, reduction in the lean mass and increase in body fat. Hydrosoluble drugs have a lower volume of distribution than lipophilic, for example. The lower quantity of albumin in the elderly also conditions the lesser availability of transporter proteins. The lower perfusion of the peripheral tissues means a lesser distribution of drugs towards them.
- Alterations in the metabolism of drugs, due basically to physiological HI at these ages (diminution of the blood flow to the liver, reduction of hepatocytes, reduction in mitochondrial enzymes).
- Alterations in the excretion and elimination processes, related with the physiological decline in creatinine clearance (up to 50% at 80 years). Excretion of drugs by this route is affected in a similar way, so that their half life can be substantially increased.

The pharmacodynamics of drugs can also be altered at these ages and it has been found that there can be a different quantity and sensibility of receptors for different drugs in the elderly, and that the homeostatic mechanisms in this age group can be altered (body temperature control, blood pressure, balance, etc.).

The use of antihistamines in the elderly is conditioned by multiple pharmacokinetic and pharmacodynamic factors, on occasions not well studied for this age group. First generation antihistamines are in general very lipophilic and cross the hematoencephalic barrier easily, which results in the possibility of adverse effects such as lack of coordination, alterations in memory,

dyskinesia, anxiety, confusion, sedation, vertigo, somnolence or the activation of epileptogenic foci. This group of antihistamines is also characterised by its anticholinergic, antiserotonergic and antidopaminergic activity, which could condition symptoms such as urine retention, arrhythmias, peripheral vasodilatation, postural hypotension, tachycardia, mydriasis, which can aggravate earlier pathologies in elderly patients [81].

The taking of first generation antihistamines jointly with monoamine oxidase inhibitors, antidepressants or other psychotropic medication can strengthen the adverse effects mentioned above, so that it is formally contraindicated.

Second generation antihistamines are differentiated from those of the first by their lesser capacity to cross the hematoencephalic barrier (less lipophilic) so that they do not affect the CNS so much, and also by their higher specificity to the H₁ receptor. This conditions a lower probability of adverse effects with respect to those of the first generation.

Some second generation antihistamines are metabolized through the liver enzymatic cytochrome P450 system, as are many other drugs, so that they can produce high plasma concentrations in patients with HI or in cases of medicinal interactions with metabolic inhibitors of this system. This type of interactions led to the appearance of mortal cases of cardiac arrhythmias with terfenadine and astemizole, and their consequent removal from the market in many countries [82]. For this reason, the regulating agencies require trials of cardiac safety for any new antihistamine.

Second generation antihistamines newly introduced have, therefore, been exhaustively investigated with regard to safety, demonstrating a very low rate of adverse effects, and are those preferred for the treatment of elderly patients. Table 7 shows the pharmacokinetic characteristics and their involvement in the elderly, the specific adverse effects of some second generation antihistamines, their contraindications and the medicinal interactions which could be significant in the elderly.

There are few specific studies on the safety of antihistamines in the population of more advanced age. Most of the recommendations are based on the pharmacological characteristics of the medicine or on notifications of pharmacovigilance. There are specific studies on the effects on the CNS in the elderly, comparing first generation antihistamines against second generation, concluding that antihistamines such as cetirizine and loratadine have less probability of producing effects on the CNS than those of the first generation [83].

The use of antihistamines in the elderly must be carried out with careful consideration of the risk-benefit ratio, according to the known adverse effects and the particular conditions of each patient. It must be borne in mind that for elderly patients multi-medication is the rule, so that topical medication is preferred where possible. First generation antihistamines must be avoided as a general rule. It is important to assess the concomitant pathologies in each case,

to see whether it is necessary to adjust the dose, especially in the case of kidney or liver failure.

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