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Comparative Tolerability of Second Generation Antihistamines

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Contents

Abstract

Second generation histamine H_1 receptor antagonists, the so-called 'nonsedating' antihistamines, have high potency and additional antiallergic properties as well as H_1 antagonism and are associated with fewer adverse effects compared with the first generation antihistamines. A number of drugs in this class are approved for use: acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, loratadine, mizolastine and terfenadine. All of them have a more favourable risk-benefit ratio with regard to the CNS adverse effects. Even those second

generation antihistamines that are not actually 'nonsedating' are less impairing than their predecessors, but not one of them is entirely devoid of CNS activity.

Under certain circumstances some antihistamines may affect cardiac repolarisation resulting in cardiovascular adverse effects. Serious cardiovascular effects have been reported with terfenadine and astemizole when they are used in high dosages or when they are given to 'at risk' patients. Animal models indicate that there might be a potential risk of cardiovascular adverse effects with other antihistamines as well. However, up to now there is no clinical evidence for this assumption, despite some confusing reports. Likewise there has been much discussion about a link between these agents and carcinogenicity. However, there is no evidence that any of the second generation antihistamines increase the risk of tumour growth in humans.

Small children, elderly patients and persons with chronic renal or liver impairment are special groups in which the individual adverse effects of the second generation antihistamines must be kept in mind. The dosage for an individual has to be modified with respect to their metabolic situation.

Despite the fact that some of the second generation antihistamines are listed in the US Food and Drug Administration pregnancy risk classification as class B, the use of second generation antihistamines should be avoided during pregnancy and they should never be administered to nursing mothers.

Taking into account their negligible CNS activity, the low incidence of cardiovascular adverse effects, their lack of anticholinergic effects and other benefits, this class of antiallergic drugs represents a definite advance in therapy.

Most of the important facts concerning the clinical safety of histamine H_1 receptor antagonists (antihistamines) have already been discussed in excellent overviews and position papers.[1-3] However, new compounds, new observations and some confusing reports demand a re-evaluation of the tolerability and safety of these drugs. Therefore, the intention of this paper is to supplement these reports by reflecting the current state of knowledge in the field and to make some practical suggestions.

Approved second generation antihistamines, individually discussed in the paper are acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, loratadine, mizolastine and terfenadine.

1. CNS Adverse Effects

Symptoms of sedation, drowsiness, fatigue, performance impairment and somnolence are the most problematic adverse effects of the first generation antihistamines. However, the second generation antihistamines are practically devoid of these sedative effects.[1,4] They exhibit lower blood-brain barrier penetration because of their lipophobic nature and high degree of protein binding.[4,5] Greater affinity and specificity for peripheral H_1 receptors may also help to explain the ability of these agents to avoid central actions.[1-5]

It is important to consider that the performance impairment experienced by the patient with an allergic condition may be caused more by the condition itself than by the drugs used to treat the allergic disease.[6] Therefore, any sedative properties of modern antihistamines should not limit their therapeutic use, since the truly threatening performance impairment results from the disorder itself. Generally, all of the second generation antihistamines can be given safely to patients who need to continue their normal daily activities, including driving.[7] Within these limits of reduced performance impairment, some compounds may produce some inconvenience in a few individuals, especially at high dosages. Apart from subjective evaluation, standardised tests like driving performance,

psychomotor tests and electroencephalogram studies demonstrate some differences among the compounds. An extensive list of references is cited in the comprehensive overview of Simons.[1] Therefore, the focus here is on the most important and recent publications only.

In summary, all the mentioned second generation antihistamines are clearly less sedating and impairing than their predecessors, but none of them is entirely devoid of CNS activity. Sedation and similar symptoms are no longer characteristic adverse effects of antihistamines, when second generation antihistamines are administered at the recommended dosage. However, it is feasible that some patients may experience performance impairment, especially when higher dosages are used. The lowest risk of sedation is seen with astemizole, ebastine, fexofenadine, mizolastine, loratadine and terfenadine.[3,4] Benefit might be obtained by switching to another agent if sedation is reported. Thus, the risk-benefit ratio of these medications should be determined on an individual basis. Table I presents a summary of the risk of performance impairment related to the use of second generation antihistamines.

1.1 Acrivastine

At the recommended dosage of 8 mg/day, somnolence is the most commonly reported adverse effect of acrivastine. Nevertheless, the occurrence of somnolence is lower than it is, for example, with clemastine or hydroxyzine.[8-10] Some studies have demonstrated a higher incidence of performance impairment in women compared with men, even at the recommended dosage.[11] Acrivastine did not affect psychomotor tests.[12]

1.2 Astemizole

At the recommended dosage, i.e. 10 mg/day, astemizole does not cause any more sedation than placebo.[5-15] No potentiating effect of alcohol (ethanol) has been seen.[13-15]

1.3 Azelastine

The oral formula of azelastine (azelastine is better known as a topical treatment) may induce occasional tiredness and minimal effects on performance or vigilance even when the recommended dosage of 2 mg/day is administered.[16,17] Yet, the clinical relevance of these effects seems to be low, similar to those seen with acrivastine.

1.4 Cetirizine

A number of investigations have demonstrated that the administration of a single dose of cetirizine 10mg does not cause sedation.[18-28] On the other hand, mild sedation or impairment of driving performance have been reported in some studies[29-32] even though the study authors themselves did not consider these effects to be of clinical relevance. Nevertheless, a dose-related incidence of sedation has been demonstrated.[33-35] Alcohol would appear to have an additive effect,[33-35] but there is also a study demonstrating the lack of this potential effect.[36] Coadministration of cimetidine inhibits the disposition of cetirizine in rabbits.[37] Administration of theophylline at a dose of >400mg can

Table I. The risk of performance impairment related to second generation antihistamines

Drug	Standard dosage	High dosage	With alcohol (ethanol)	Clinically relevant
Acrivastine	Possible	Yes	Yes	Yes
Astemizole	No	No	No	No
Azelastine	Possible	Yes	Yes	Yes
Cetirizine	No	Yes	Possible	No
Ebastine	No	Possible	No	No
Fexofenadine	No	No	No	No
Loratadine	No	Possible	No	No
Mizolastine	No	No	No	No
Terfenadine	No	No	No	No

induce a slight clearance decrease in cetirizine resulting in elevated serum concentrations of cetirizine and at the same time somnolence, fatigue and dry mouth. Taken together, the published results, although equivocal, suggest that cetirizine may be more sedating than loratadine or the new compounds fexofenadine and mizolastine, but is less sedating than ketotifen or older antihistamines.

1.5 Ebastine

The administration of ebastine at the recommended dosage of 10 mg/day is more likely to produce a stimulating effect than a sedating one.[11] The incidence of adverse events with ebastine is similar in patients treated with 10 or 20 mg/day and does not differ significantly from the incidence reported in placebo recipients.[38-40] However, dose-dependent sedation does occur if an ebastine dose of ≥20mg is administered.[41,42]

1.6 Fexofenadine

Fexofenadine is the active metabolite of terfenadine and therefore the sedating effect of this compound is the same as that of terfenadine, i.e. it is negligible.[43-45] Even fexofenadine given at twice the recommended dosage of 120 mg/day in combination with alcohol does not induce sedation.[46]

1.7 Loratadine

No significant sedation was observed after the administration of either single doses of loratadine 10mg and 20mg or 10 mg/day administered for a number of days in several studies.[47-49] No change has been seen in electroencephalogram studies, even after the administration of high dosages. No potentiating effect of alcohol has been observed, nor has a detectable effect on overall flying performance.[50] However, loratadine has been shown to have an impairing effect on performance when it is given over a number of days at twice the recommended therapeutic dosage of 10 mg/day.[11] The occurrence of a dose-related somnolence has also been reported in some clinical trials,[51-53] but the clinical relevance of these observations seems to be questionable.

1.8 Mizolastine

No sedation occurs after mizolastine is administered at the recommended dosage of 10 mg/day.[54] In animal models, mizolastine has been compared with astemizole, cetirizine, loratadine and terfenadine.[54] The intravenous administration of extremely high doses (up to 10 mg/kg) produced sedation with the comparison drugs but not with mizolastine.[54] Patat et al.[54] concluded that mizolastine appears to be devoid of sedative effects. In humans, no significant interaction has been seen between alcohol or lorazepam and mizolastine.[55] No impairment in actual driving tests has been seen with mizolastine when the recommended dosage is administered.[11,36,56] In contrast, in studies where doses of 20 to 75mg were given, some impairing effect was seen.[11,57-59] Overall, the compound seems to be very well tolerated at therapeutic dosages, although adverse effects in individual patients cannot be completely ruled out.

1.9 Terfenadine

It has been clearly demonstrated that the administration of up to 2 times the recommended dosage of terfenadine of 60 mg/day does not cause sedation.[60] However, administration of terfenadine 120mg twice daily over a number of days did produce a significantly impairing effect.[11] No potentiating effect with alcohol has been observed and there is no detectable effect on flying performance.[61]

2. Cardiovascular Adverse Effects

Under certain circumstances some antihistamines may affect cardiac repolarisation resulting in cardiovascular adverse effects.[1,62,63] These cardiovascular effects with second generation antihistamines occur extremely rarely considering the extensive use of these agents. However, there have been reports of terfenadine and astemizole pro-

longing the corrected QT (QTc) interval leading to ventricular arrhythmias. Triggers for these fatal events were drug overdose, concomitant administration of drugs that inhibit the cytochrome P450 (CYP) enzyme system (for example, macrolide antibacterials, itraconazole and ketoconazole), presence of hepatic dysfunction (cirrhosis), cardiac abnormalities (congenital prolongation of the QT interval, ischaemic heart disease, congestive heart failure) or severe electrolyte disturbance (hypokalaemia, hypomagnesaemia or hypocalcaemia).[64-66] As far as is currently known, the blockade of the potassium channel, especially the delayed rectifier current, seems to be the hallmark of the proarrhythmic effects of the second generation antihistamines.[67-69] Nevertheless, it must be borne in mind that the risk of cardiovascular effects with terfenadine (which is the highest within this group) was found to be similar to, or lower than, the risk of cardiovascular effects with the first-generation antihistamines.[70-72]

In addition to an increase in the QTc interval, a number of other cardiovascular abnormalities have been linked to antihistamine use. These abnormalities include notched or inverted T waves, prominent U waves or TU waves, nonspecific ST-T wave abnormalities, first- and second-degree atrioventricular block, Mobitz type II heart block, right or left bundle branch block, premature beats, ventricular ectopic beats, ventricular tachycardia or fibrillation and pause-dependent torsade de pointes.

Most antihistamines are metabolised through the hepatic CYP enzyme system. In particular, the second generation antihistamines are metabolised by the isoenzyme CYP3A4.[66,73,74] However, while the compounds are preferentially metabolised by CYP3A4 in humans, they can also be metabolised by CYP2D6 in the presence of CYP3A4 inhibitors.[74,75] The occurrence of cardiovascular effects following an overdose or the concomitant administration of a CYP inhibitor is caused by accumulation of the compound inducing blockade of the potassium channels.

In addition, histamine itself possesses arrhythmogenic effects, increasing sinus rate and ventricular automaticity and slowing atrioventricular conduction.[76] It also may interfere with depolarisation and repolarisation through its effect on calcium and potassium currents.[76] Consequently, the direct activation of histamine receptors can induce cardiac arrhythmias. These histaminergic effects may explain the arrhythmogenic effect described for some antihistamines.[63] However, despite gaining some subtle results using animal models, the predictiveness of the available models must be critically evaluated since the outcome of studies is clearly model-dependent.

The publication of a study of spontaneous adverse drug reactions reports from the WHO database for acrivastine, astemizole, cetirizine, loratadine and terfenadine[77] lead to some insecurity in the use of all second generation antihistamines. It is unclear whether cardiovascular adverse events may be a class effect, but, taking into consideration the comments that were published in response to the study,[78,79] we believe that to date there is no definitive evidence for a causal association between the second generation antihistamines (with the exception of astemizole and terfenadine) and ventricular tachyarrhythmias. However, to date many of the drugs have not been carefully evaluated for their true potential to cause arrhythmias in humans and some of them have only been available for use for a short time and therefore extensive clinical experience is lacking for these agents.

In summary, terfenadine and astemizole have rarely been associated with serious cardiovascular effects. These effects become apparent either when the drug is administered at high dosages or when it is given in therapeutic dosages to 'at risk' patients. Despite some confusing reports,[77-79] it is not proven that other second generation antihistamines cause life-threatening cardiovascular events. However, many of the drugs have not been carefully evaluated for their true potential to cause arrhythmias in humans.

In our view, the unquestionable benefit of the second generation antihistamines over the first generation agents is definitely not mitigated by possible cardiovascular adverse events. Terfenad-

ine and astemizole are the only agents proven to have some risk. Therefore, it would seem easiest and safest to avoid use of these drugs. On the other hand, keeping to the recommended dosage and excluding patients 'at risk' – that is patients with pre-existing cardiovascular disease, hepatic dysfunction or patients who are taking concomitant medication with drugs that inhibit the CYP enzymes – could be an appropriate course of action. Regulatory action with regard to these drugs has been taken in various markets to ensure their appropriate use (see sections 2.2 and 2.9). Table II presents a summary of the potential risk of cardiovascular adverse events related to the use of second generation antihistamines.

2.1 Acrivastine

Acrivastine is not metabolised in the liver to any great extent and is excreted in the urine and faeces as an unchanged drug. Therefore, neither impaired hepatic function nor the concomitant administration of a CYP inhibitor increase the risk of cardiovascular adverse effects.[80] The agent appears to be well tolerated from the view point of cardiovascular adverse effects.[80]

2.2 Astemizole

Although the propensity of astemizole alone to produce QTc interval prolongation is not as great as that of terfenadine, numerous case reports of delayed cardiac repolarisation related to use of astemizole and its metabolites have been published.[65,81-93] At least 2 metabolites (desmethyl astemizole and norastemizole) and astemizole itself can accumulate in the plasma (especially if the CYP3A4 isoenzyme system is disturbed) and can induce the blockade of multiple human cardiac potassium currents.[94] However, the individual role of the metabolites in the induction of cardiovascular adverse events is less clear and making it difficult to be sure which of the agent's actions are really responsible for the cardiac adverse events. As well as CYP–inhibiting drugs, the coadministration of the following drugs is contraindicated: antiarrhythmics, tricyclic antidepressants, dofetilide,[95] sotalol, haloperidol, thioridazine, probucol, cisapride, bepridil and pentamidine.[96] Astemizole is now a prescription-only medication in the UK and the labelling of astemizole has been modified in the US regarding cardiovascular adverse events, anaphylaxis and potentially serious drug interaction.

2.3 Azelastine

No cardiovascular adverse events have been reported to date with azelastine. The drug seems to be well tolerated in this respect.[16,97]

2.4 Cetirizine

Cetirizine is not metabolised by the liver to any great extent and is excreted in the urine and faeces as unchanged drug. Therefore, impaired hepatic function or the coadministration of a CYP inhibitor would not be expected to increase the risk of cardiovascular adverse effects with this drug.[98,99] Experimental evidence shows that cetirizine is unlikely to cause cardiotoxic effects,[63,100-102] al-

Table II. The potential risk of cardiovascular adverse effects

	Blockade of potassium channel	P450 metabolism	Experimental evidence	Clinically relevant
Acrivastine	No reports	No	No reports	No
Astemizole	Yes	Yes	Yes	Yes
Azelastine	No reports	Yes	No reports	No
Cetirizine	No	No	In animal model	No
Ebastine	Possible	Yes	In animal model	Unlikely
Fexofenadine	Possible	No	No	Unlikely
Loratadine	No	Yes	No	No
Mizolastine	No	Yes	No	Unlikely
Terfenadine	Yes	Yes	Yes	Yes

though it is possible to demonstrate proarrhythmic activities in animal models.[103] Concurrent use of ibutilide can induce arrhythmia (elongation of QT interval). Despite widespread use of this agent, only a number of single cases of arrythmia, palpitations, tachycardia and similar have been reported to the UK's Medicines Control Agency Adverse Drug Reactions Online Information Tracking (ADROIT) database.

2.5 Ebastine

The chemical structure of ebastine (it is a piperidine derivative) and its metabolism closely resembles those of terfenadine. The compound is transformed into the active acid metabolite during first-pass metabolism. Although ebastine suppresses the slowly activating potassium current and induces a prolongation of the QTc interval in a dose-dependent manner, as demonstrated in a guinea pig model[101,104] to date there is no evidence that this effect is of any clinical relevance. In a sensitive experimental model for detecting prolongation of the QTc interval no significant effects were observed after ebastine administration.[105] Coadministration of ebastine with either erythromycin or ketoconazole results in increased accumulation of the parent drug in plasma. However, no correlation between QTc interval change and plasma concentration of ebastine or its metabolite has been observed.[106] No clinically relevant cardiac events have been observed with ebastine to date.

2.6 Fexofenadine

As fexofenadine itself is the active metabolite, there is no noteworthy metabolism in the liver. Therefore, the presence of impaired hepatic function or concomitant administration of a CYP inhibitor would not be expected to increase the risk of cardiac adverse effects. *In vitro*, the blocking effect of fexofenadine on a cloned delayed rectifier potassium channel from the human heart is 583 times less potent than that of terfenadine.[62] In sensitive experimental models for detecting the prolongation of the QTc interval no significant effects were observed following administration of fexofenadine.[105,107] In a clinical study involving healthy volunteers, fexofenadine had no significant effect on QTc, even at dosages more than 10 times higher than the recommended dosage.[108] To date, there has been 1 report of adverse cardiac effects associated with fexofenadine.[109] A 67-year-old man had a history of mild cardiac disease. After 2 months' treatment with fexofenadine 180 mg/day he had an episode of syncope and demonstrated a prolonged QT interval. When fexofenadine was discontinued, the man's QT interval shortened; however, it increased again and culminated to ventricular fibrillation when fexofenadine was restarted. He completely recovered after defibrillation and discontinuation of fexofenadine. The authors of the case report believe that there was a causal relationship between the episodes and drug intake.

2.7 Loratadine

The potential of loratadine to suppress potassium channels is extremely low and of no clinical relevance. The suppression occurs at concentrations which are between 1000 and 5000 times higher than the concentrations obtained after administration of the recommended dose of 10mg.[104] In an experimental guinea-pig model loratadine is devoid of ECG or cardiovascular effects.[48,49,101,102] In long term studies using concentrations of loratadine 5 times higher than those recommended, there were no statistically significant changes in any ECG parameter.[110] Concomitant administration of erythromycin did not lead to the occurrence of cardiovascular adverse effects (for example, QT interval elongation).[111] Plasma concentrations of loratadine were increased following the coadministration of therapeutic dosages of erythromycin (by 40%), cimetidine (by 103%) and ketoconazole (by 307%) due to the impaired hepatic metabolism of loratadine, but no clinically relevant changes in the safety profile of the agent could be observed (i.e. no cardiac effects, no sedation and no syncope).[112] The plasma concentrations of cimetidine and ketoconazole were not influenced and the plasma concentration of erythromycin was decreased by 15% with the

coadministration of loratadine.[112] Furthermore, concurrent administration of ritonavir and loratadine leads to a 3-fold increase in the area under the concentration-time curve (AUC) of loratadine.[112] The clinical relevance of these observations is unknown.

Despite widespread use of this agent only a number of single cases of arrythmia, palpitations, tachycardia and similar have been reported to ADROIT.

2.8 Mizolastine

Mizolastine is a relatively new astemizole derivative, but it is devoid of cardiovascular effects. In several clinical trials there was no indication of any cardiovascular adverse events.[59,113,114] A study in volunteers confirmed the lack of cardiovascular effects of mizolastine at dosages up to 4 times the therapeutic dosage and in particular the absence of any effect on the ventricular repolarisation.[115] In the guinea pig model, mizolastine has been shown not to influence the delayed rectifier current.[116] To date, no clinically relevant cardiac events have been observed.

2.9 Terfenadine

The first of many reports of cardiovascular adverse events appeared in 1989.[64,117-120] Concurrent administration of terfenadine and CYP inhibitors was associated with an increased risk of QTc prolongation.[121-123] The parent drug, which has a quinidine-like action, blocks the delayed potassium rectifier current of ventricular myocites with a consequent delay in cardiac repolarisation causing prolongation of the QTc interval and arrhythmias.[66,67,124,125] The active metabolite of terfenadine, terfenadine carboxylate is devoid of these activities which contrasts with the metabolites of astemizole.

It is important to consider not only drug-drug interactions but also drug-food interactions. The drug interaction of terfenadine with grapefruit juice has lead to fatalities.[126-128] Grapefruit juice can be expected to have virtually the same effects as erythromycin, ketoconazole or itraconazole on a number of drugs. There is a widespread misconception that an unusually large amount of grapefruit juice is required to have an effect; this is not true. Spencer[128] reported a case of a 29-year-old man who experienced a fatal interaction between terfenadine and 2 glasses of grapefruit juice. The effect appears to be the result of a significant inhibition of the gut wall CYP3A4, which is important in metabolism of all dihydropyridine compounds like terfenadine. However, there is a study which shows that astemizole is not affected to a significant extent by grapefruit juice because it is metabolised by several CYP isozymes.[128]

Terfenadine-containing products have been removed from the US market because of cardiac complications when the drug is used with other agents and the availability of fexofenadine. The European Commission has withdrawn terfenadine 120mg products from the European markets and the labelled warnings have been strengthened on the lower dose products.

3. Carcinogenicity

Generally, drugs inhibiting the CYP enzyme system have some potential to enhance tumour growth.[129] Most of the discussions concerning the carcinogenicity of second generation antihistamines refer to findings of Brandes et al.[130] These authors found that loratadine and astemizole administered in low and medium dosages, but not in high dosages, increased the growth of melanoma cells and fibrosarcomas in mice. Cetirizine was found not to affect the growth of either tumour type. Mathews[131] could not confirm these results. In his trial, Mathews[131] did not find any evidence that loratadine increased tumour growth *in vitro* or in rodents.

On the other hand, higher dosages of antihistamines can possibly augment the effect of anticancer drugs.[132,133] Other studies suggest a protective effect of antihistamines because histamine can stimulate cell division and activate suppresser T cells, which downregulate the immune system.[134,135] However, it seems possible that hista-

mine can augment as well as inhibit tumour growth.[136]

These data are interesting from an experimental point of view, even though they are not consistent. However, clinical experience over the past 50 years does not point to any link between antihistamines and cancer.[3] Therefore, the US Food and Drug Administration (FDA) has not recommended any modification to the clinical use of antihistamines.[137]

In summary, no link between antihistamine treatment in humans, and carcinogenicity has ever been suspected. There is no evidence that any of the second generation antihistamines should be avoided because of a potential to increase the risk of tumour growth in humans.

4. Adverse Effects in Special Groups

4.1 Small Children

For most of the second generation antihistamines, safety data are not established for children under 12 years of age. In children, metabolic functions are not as effective as in adults. Metabolic functions become more and more effective from the time of birth until adolescence. For that reason a given second generation antihistamine possibly needs longer time for onset of action, it reaches comparably high serum concentrations, it can cross the blood-brain barrier more easily and is excreted slower than in adults. These factors increase the likelihood of children experiencing adverse effects. As for other medications that are designed for adults and are also given to children, the dosage of antihistamines needs to be modified.

In summary, it is no problem to use second generation antihistamines in children aged between 3 and 12 years old, although only single papers are published on this topic. Related to the metabolic situation, the dosage has to be reduced in children aged 3 to 12 years. For children aged between 6 and 12 years, half of the adult dosage is often enough. For small children aged between 3 and 5 years there are several specially developed preparations commonly administered as syrup. In children over 12 years old, all of the second generation antihistamines can be administered at the same dosages as are used in adults. When an appropriate dosage is administered there is no evidence of serious adverse effects with any of the new drugs.

4.2 Elderly Patients

Elderly patients may be more susceptible than the young to the potential sedating and anticholinergic effects of antihistamines. This is the result of a slight decrease in renal and liver function in the elderly which delays the metabolism of the antihistamines. This leads to increased serum concentrations of the given medication compared with younger patients. Second generation antihistamines are lipophobic and do not readily cross the blood-brain barrier.[138] For that reason they generally exhibit fewer CNS adverse effects than first generation antihistamines in elderly patients because of their selective effect on peripheral H_1 receptors rather than the central H_1 receptors.[139] Avoiding an overdose will help to prevent CNS and cardiovascular adverse effects in elderly patients.

In summary, no specific adverse events need to be considered in elderly patients. However, the patients are more susceptible to adverse effects because of delayed metabolism. To reduce the risk of adverse events we recommend that treatment is started at half the recommended dosage or by giving the recommended dosage every other day.

4.2.1 Acrivastine

No dosage recommendation for acrivastine in elderly patients is available. No special risks of adverse events have been mentioned but an increase in elimination half-life of acrivastine by 35% has been demonstrated.[140] Acrivastine is excreted mainly with the urine. Renal impairment in the elderly therefore needs to be taken into account.

4.2.2 Astemizole

There is no indication that the metabolism of astemizole is altered in the elderly. Consequently, no dosage modification is necessary. However, care should be taken to avoid an overdose or the concomitant administration of macrolide antibac-

terials, ketoconazole or itraconazole etc., as increased plasma concentrations can lead to severe cardiovascular adverse effects[139] even in patients with no increased risk of cardiac arrhythmias.

4.2.3 Azelastine

No special considerations with azelastine are required for administration in the elderly and no dosage modification is necessary.

4.2.4 Cetirizine

There are no differences in the metabolism of cetirizine for patients aged <65 years old with the exception of a reduced clearance of the agent in proportion to the age-related reduction in creatinine clearance. A reduction in clearance by 40% and an increase in the half-life by 50% has been documented.[141,142] As a consequence elevated serum concentrations of cetirizine could lead to an increased risk of adverse effects like sedation, dry mouth, etc. In contrast, and surprisingly, Gengo and Kinkel[143] described in a recent study that after 7 days of cetirizine therapy in elderly patients performance improved compared with placebo.

4.2.5 Ebastine

The pharmacokinetic properties of the active metabolite of ebastine, carebastine, in elderly generally do not differ from those in younger adults.[144,145] Consequently, the risk of adverse events is comparable in elderly patients.

4.2.6 Fexofenadine

According to the manufacturer's recommendations, no special considerations are necessary when prescribing fexofenadine to elderly patients. However, it is likely that the dosage of fexofenadine should be reduced in elderly patients because of reduced renal clearance. In addition, adequate evaluation of this drug in the elderly has not been completed.

4.2.7 Loratadine

It has been reported that in healthy elderly patients the peak plasma concentrations of loratadine can be 50% greater than those in younger individuals, and that the half-life increases from 8.2 hours to up to 18.2 hours. Therefore, elderly patients can experience somnolence caused by increased plasma concentrations of loratadine.[139] However, no serious cardiovascular adverse effects have been reported following the use of loratadine in elderly patients to date.[139]

4.2.8 Mizolastine

Patat et al.[146] studied the effect of a single 10mg dose of mizolastine on psychomotor performance and memory in 15 elderly patients. The drug did not induce subjective drowsiness or impairment in psychomotor performance and short and long term memory. Furthermore, the pharmacokinetic profile of the drug was comparable to that observed in healthy young volunteers. For this reason mizolastine seems to be well tolerated in the elderly and current knowledge indicates that no dosage adjustment is necessary for patients aged >65.

4.2.9 Terfenadine

Terfenadine may cause minimal if any sedation and little impairment in cognitive and psychomotor activity in elderly patients. Gengo and Kinkel[143] reported unchanged cognitive function in elderly patients after 7 days' treatment with terfenadine. Terfenadine can cause serious cardiovascular adverse effects, following an overdose or after co-administration with ketoconazole, itraconazole or macrolide antibacterials.[139] Therefore, terfenadine should be replaced by fexofenadine in the elderly.

4.3 Chronic Renal or Liver Impairment

For most of the second generation antihistamines only about 10 to 20% of the dose administered is excreted in the urine.[147,148] The exceptions are acrivastine and cetirizine; for these agents about 60% of the dose administered is excreted in the urine.[147,148] Renal function can be impaired by the presence of kidney disease and becomes impaired with age. In the presence of severely impaired renal function, a given antihistamine has a markedly longer excretion half-life and serum concentrations become elevated. For this reason, patients with impaired renal function are at greater risk of dose-dependent adverse effects.

The second generation antihistamines are commonly metabolised in the liver by the CYP enzyme system.[147,148] Thus, impairment of liver function as well as concomitant treatment with agents that are metabolised by the same system can lead to increased serum concentrations of the given antihistamine and an increased risk of adverse effects. Several agents affecting the CYP enzyme system are listed in section 2 and the data are summarised in table II.

In summary, for most of the second generation antihistamines only about 10 to 20% of the dose administered is excreted in the urine; the exceptions are acrivastine and cetirizine (about 60%). The second generation antihistamines are commonly metabolised in the liver by the CYP enzyme system. Thus, coadministration of antihistamines and agents that compete with the CYP enzyme system should be avoided. In patients with renal or hepatic impairment modification of the dosage is necessary and use of certain concomitant medications should be avoided. In general, patients should begin treatment with half the recommended dosage.

4.3.1 Acrivastine

For acrivastine, adjustment of the dosage may be indicated, although no specific recommendations are available for either patients with renal failure or patients with liver failure.

4.3.2 Astemizole

For astemizole, no dosage adjustments are required in patients with renal impairment.[149] The use of the agent should be carefully considered in patients with liver dysfunction and in patients receiving treatment with structurally similar drugs such as macrolide antibacterials, itraconazole and ketoconazole.

4.3.3 Azelastine

For azelastine, dosage adjustment may be indicated, although no specific recommendations are available.

4.3.4 Cetirizine

For cetirizine, 60% of a dose is excreted unchanged by the kidney within the first 24 hours following administration. Part of the dose is metabolised by the liver. This route of elimination is delayed in patients with impaired liver function and elevated serum concentrations have been demonstrated,[148] leading to transient sedation. Wood et al.[98] found that hepatic impairment (cirrhosis) can lead to a 40% decrease in clearance. A dosage adjustment is also necessary for patients with moderate or severe renal impairment or patients receiving dialysis. A 70% clearance decrease has been found in patients with renal impairment.[141] Haemodialysis can remove a maximum of 10% of the dose administered.[150]

4.3.5 Ebastine

For ebastine no dosage adjustments are required in patients with renal impairment. Nevertheless, we recommend caution when administering ebastine to patients with hepatic or renal impairment.[106]

4.3.6 Fexofenadine

For fexofenadine no dosage adjustments are required in patients with either renal or hepatic impairment.

4.3.7 Loratadine

For loratadine a dosage adjustment is necessary in patients with moderate or severe renal impairment (i.e. creatinine clearance ≤30 ml/min) and in patients receiving dialysis. An increase in plasma peak concentration by 73% has been found. Haemodialysis cannot remove the given dose. Patients with moderate to severe renal impairment and those receiving dialysis are at greater risk of experiencing somnolence.

Hepatic impairment (e.g. cirrhosis) can lead to a doubling of the plasma peak concentration and an increase in the half-life to 24 hours. Patients with hepatic impairment are at increased risk of experiencing somnolence.

Schiano et al.[151] described 2 patients who experienced subfulminant liver failure and severe hepatotoxity related to loratadine use. Liver toxicity has only been reported in single patients, but clinicians should bare in mind the possibility.

4.3.8 Mizolastine

No dosage adjustments are suggested in patients with renal or hepatic impairment. However, mizolastine should be used with caution (like astemizole) in patients with hepatic impairment until more data on safety are available.

4.3.9 Terfenadine

A dosage adjustment may be indicated in patients with liver dysfunction, although no specific recommendations are available. In patients with liver dysfunction, concomitant use of structurally similar drugs like macrolide antibacterials, itraconazole, ketoconazole, should be avoided. In general, the use of terfenadine should be evaluated critically.

4.4 Pregnancy and Nursing

Antihistamines cross the placenta, but there is no evidence to date that second generation antihistamines cause fetal anomalies in humans. Due to the lack of representative studies most of the new antihistamines are classified as pregnancy FDA category C or B.[152][1] Therefore, they should be given only if the expected benefits exceed the possible risks to the fetus. It is likely that all of the antihistamines are excreted in breast milk, although evidence for this is scanty and available only for some agents, e.g. promethazine.[153]

In summary, loratadine and cetirizine are ranked in FDA pregnancy risk classification as B. Nevertheless, we recommend that second generation antihistamines are not used during pregnancy if possible. Taking into account the FDA pregnancy risk classification, class B second generation antihistamines may be used in selected patients who are pregnant, taking into consideration the risk-benefit ratio, but never in nursing mothers because it is likely that the drug is excreted in breast milk. However, because of more experience with first generation antihistamines in pregnancy, the use of these agents is preferred in this setting[152] if a prescription of an oral treatment seems to be essential.

4.4.1 Acrivastine

The risk of teratogenicity with acrivastine cannot be completely ruled out because of the lack of representative studies.

4.4.2 Astemizole

Astemizole is classed as FDA category C and the FDA has stated that astemizole is not likely to be carcinogenic in humans.[154] However, there are no adequate data that assess potential teratogenic effects of this agent. In animal studies, a milk-plasma ratio of 4.4 has been reported for astemizole.[155] Ito et al.[156] found no severe adverse effects in neonates exposed to astemizole via breast milk. No teratogenic effects were seen in rats and rabbits given 200 times the maximum human dosage.[157] However, in our opinion use of this agent should be avoided in pregnancy.

4.4.3 Azelastine

Azelastine is rated as FDA category C and the manufacturer recommends that use of the drug is avoided in nursing mothers.[16]

4.4.4 Cetirizine

Cetirizine is rated as FDA category B. However, no adequate studies have been carried out in pregnant women to date. Einarson et al.[158] did not find any increased teratogenic risk. Use in nursing mothers is not recommended. In mice, pup bodyweight gain has been shown to be retarded following *in utero* exposure and studies in beagles show that 3% of the dose administered is excreted in breast milk.

4.4.5 Ebastine

The risk of teratogenicity cannot be ruled out with ebastine because of the lack of representative studies.

1 The safety of drugs in pregnancy is commonly divided into 5 categories by the US Food and Drug Administration (A, B, C, D, X) indicating the potential for systemic absorption, and animal and human reports of birth defects. The definition of category B is: animal studies show no risk, but human studies are inadequate, or animal studies show some risk that is not supported by human studies. The definition of category C is: animal studies show risk, but human studies are inadequate or lacking, or there are no studies in animals or humans.

4.4.6 Fexofenadine

The risk of teratogenicity cannot be ruled out with fexofenadine because of the lack of representative studies. Fexofenadine is classified as FDA category C.

4.4.7 Loratadine

Loratadine is classed as an FDA category B agent. However, to date no adequate studies in pregnant women have been performed. Loratadine and its active metabolite descarboethoxyloratadine pass easily into breast milk and achieve concentrations equivalent to plasma concentrations. The dose received by the breast-fed infant is about 0.46% of the dose given to the mother.[159] Therefore, care is needed when loratadine is given to nursing mothers.

4.4.8 Mizolastine

The risk of teratogenicity cannot be ruled out with mizolastine because of the lack of representative studies.

4.4.9 Terfenadine

Terfenadine may be used in pregnant women without the risk of inducing severe adverse effects in exposed neonates.[156,160] No teratogenic effects were seen in rats and rabbits exposed to 300 and 500 times the maximum human dose.[157,161] However, no adequate studies have been performed in pregnant women to date.

5. Bodyweight Gain

There is very little published on the relationship between bodyweight gain in connection with treatment with second generation antihistamines. However, it has been observed that astemizole treated patients tend to experience an increase in bodyweight and appetite (3.6% of patients) not only because of the well-being due to the symptom reduction but also because of appetite stimulation.[162] The appetite stimulation may be due to the direct H_1 receptor antagonism on the hypothalamic centre, suggesting a selective action on central H_1 receptors.

The incidence of bodyweight gain and increased appetite is much lower in other second generation antihistamines. For example, the incidence of bodyweight gain is 0.4% for cetirizine, bodyweight gain has not been described for ebastine, only single case reports are known with loratadine treatment and bodyweight gain has not been reported with mizolastine.[32,38,113]

In summary, some astemizole treated patients may experience bodyweight gain and an increased appetite. Besides astemizole, bodyweight gain is not considered of clinical relevance.

6. Conclusion

The second generation antihistamines appear to have a more encouraging risk-benefit ratio than the first generation antihistamines. The lack of anticholinergic effects and the negligible CNS activity are important. Cardiovascular adverse events occurring following an overdose or under specific conditions are of clinical relevance for astemizole and terfenadine. However, like all classes of medications, a careful individual evaluation is required to select the most appropriate treatment for the individual patient.

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